Patented Dec. 21, 1948 2,457,024

UNITED STATES PATENT OFFICE

2,457,024

COLLAPSIBLE TUBE HOLDER

Claus Arp, San Francisco, Calif.

Application February 13, 1945, Serial No. 577,603

2 Claims. (Cl. 248—108)

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This invention relates to a novel and improved holder for a collapsible tube of the type used for packing and subsequently dispensing creams, pastes, and similar commodities, the same being so designed and constructed as to expedite assured dispensing of the entire usable contents from said tube.

Briefly, the preferred embodiment of the invention is characterized by a base plate having a lateral adapter at one end, the latter to accommodate the usual screw capped discharge neck of the tube, said plate having, at the opposite end, a slidable clip fashioned to securely clamp the cleated end or butt of the tube in a manner to facilitate expressing of the contents from the latter by pressure from the thumb of the user.

Structurally speaking, one phase of novelty has to do with the aforesaid plate, this being of elongated rectangular form and provided at the dispensing end with a laterally bent adapter the latter being so made as to effectively receive and hold in place the capped discharge end of the tube.

Novelty is also predicated upon the anchoring and chock fixture or clip, this being constructed for slidable use on said plate and having a portion saddled over the adjacent end of the tube to serve in a manner to be hereinafter specifically described.

Other features and advantages will become readily apparent from the following description and the accompanying illustrative drawings.

In the drawings, wherein like numerals are employed to designate like parts throughout the views:

Figure 1 is a perspective view of a collapsible tube holder constructed in accordance with the principles of the present invention, showing the manner in which it functions.

Figure 2 is a side elevational view of the same.

Figure 3 is a top plan view.

Figure 4 is a perspective view of the slidable anchoring and chock clip.

Referring now to the drawings by distinguishing reference numerals, it will be seen that the base plate, as a unit, is denoted by the numeral 5, while the slidable chock clip is denoted by the numeral 6.

The plate comprises an elongated, flat, rectangular body portion 7 whose outer end is bent, as at 8, to define a limited curvate transversely disposed bend 9. The terminal is bent laterally to assume a position at right angles to the body, this as indicated at 10. The terminal 10 is cut out or notched, as at 11, and therefore functions

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as a keeper and adapter for the capped discharge neck 12 of the conventional collapsible tube 13. The adapter may be said to be substantially horseshoe-shaped in configuration, and it embraces the neck in the manner shown in the drawings.

The retaining and chock clip 6 coacts with the usual closing cleat 14 on the compressible end portion 15 of the tube. This clip is characterized by an intermediate portion 16 which saddles over the cleat 14 and a pair of V-shaped limbs or arms 17 which underlie the plate for assembling and retention purposes. The arms terminate in hook-like holders 18 which engage over the top surface of the plate as illustrated.

It is evident that, in use, the tube is placed flat on the body 7 of the plate. The capped neck is fitted through the opening in the horseshoe-like adapter 10, the latter then serving to retain said neck-equipped end in place as the contents is expunged therefrom. The clip 6 is slipped over the opposite end of the plate and held slidably in position by the coacting hooks 18 and detents 17. The central portion of the clip is laterally offset and engages over the end portion 15 of the tube inwardly of the cleat 14. Thus, in using the device, a thumb of the user is pressed against the area 15 when the cap is removed, whereby the cream, paste, or other contents are squeezed out in the customary manner. As the cleated end is flattened by expunging of the cream from the tube, the clip is slid along to serve as a follower and chock, as is evident. In other words, said clip holds the cleated end down on the plate and also prevents the contents from "backing up" into said cleated end after once expressed therefrom. It is evident that the clip is not a squeezing device, but merely a tube-end retainer follower and chock means.

It is thought that persons skilled in the art to which the invention relates will be able to obtain a clear understanding of the invention after considering the description in connection with the drawings. Therefore, a more lengthy description is regarded as unnecessary.

Minor changes in the shape, size and arrangement of details coming within the field of invention claimed may be resorted to in actual practice, if desired.

I claim:

1. As a new article of manufacture and as a component part of a collapsible tube holder of the class described, an elongated flat plate forming a collapsible tube accommodating and supporting base, said plate being fashioned and

formed at one end into a transverse, curvilineal bend, said bend including a bight portion projecting laterally from and disposed on a plane below the underside of the plate and a limb portion of the bend terminating in a laterally directed portion apertured and forming a horseshoe-shaped tube neck adapter, said adapter being at right angles to the plate to accommodate and permit passage of said neck equipped end and the opposite end portion of said plate being rectilinearly straight, longitudinally viewed, and transversely flat in order to accommodate a slidably mounted manually shiftable tube anchoring clip.

2. A collapsible tube holder of the class described comprising an elongated flat plate forming an accommodating base for the collapsible tube, said plate terminating in an apertured projection disposed at right angles to the plate and serving to accommodate the usual neck and cap equipped end of said tube, and a wire clip bent between its ends to provide a substantially U-

shaped saddle, said saddle being engageable with an adjacent end portion of the tube when the tube is in place on said plate, said clip including a pair of opposed and coacting V-shaped detents, the free ends of the wire being fashioned into hooks and said hooks being engageable with and slidable on the longitudinal edge portions of the plate.

CLAUS ARP.

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Aug. 8, 1961 D. M. ASHKENAZ 2,995,308

JET STREAM DISPENSER

Filed Sept. 23, 1958

FIG. 1

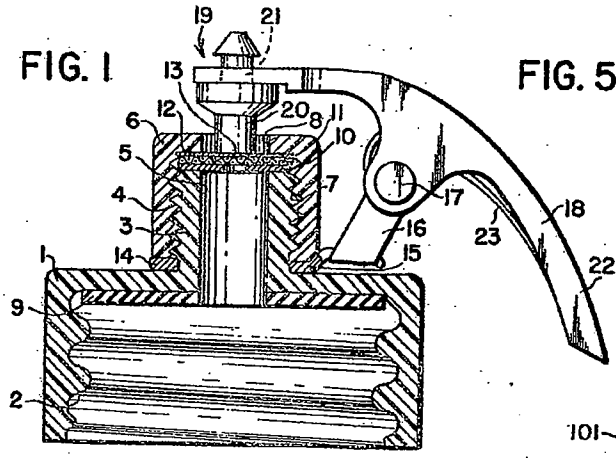


FIG. 5

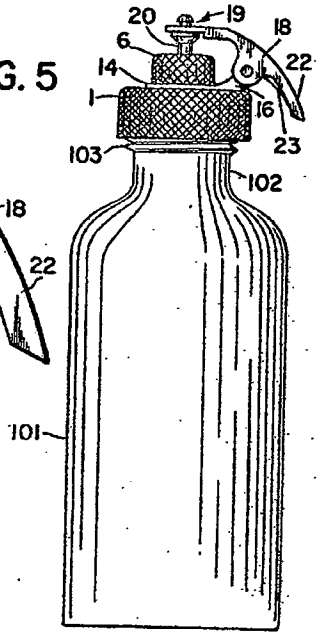
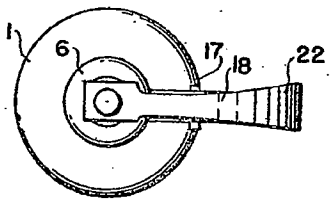


FIG. 2



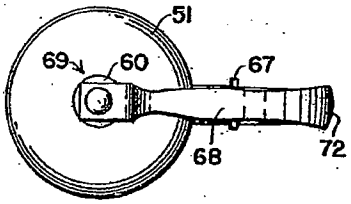


FIG. 4

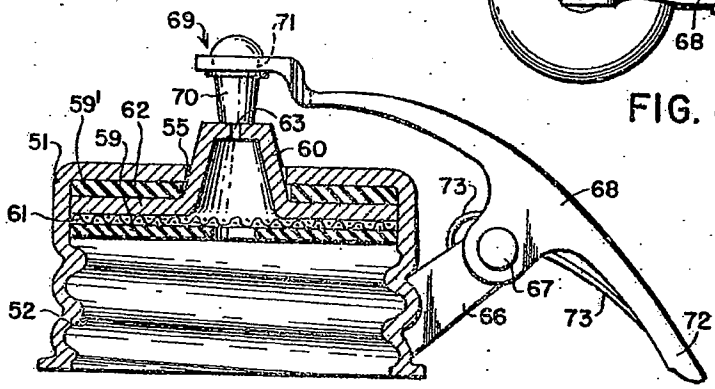


FIG. 3

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MP0185

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2,995,308

JET STREAM DISPENSER

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Filed Sept. 23, 1958, Ser. No. 762,880
5 Claims. (Cl. 239—302)

This invention relates to a jet stream dispenser which may serve as a closure for a container of volatile refrigerant used for inducing local anesthesia or analgesia in minor surgery.

It has long been the practice in minor surgical procedures to project a fine stream of a volatile refrigerant, such for example as ethyl chloride, on the operative area, where the evaporation of the refrigerant sufficiently cools the tissues to produce a desired degree of local anesthesia or analgesia.

The refrigerant, which has a vapor pressure slightly higher than atmospheric at room temperature, is ordinarily sold in small glass bottles of, say, four ounce capacity, closed by a valved cap. In use, the bottle is tipped so that the liquid contents fill the neck and the valve is opened, permitting a jet of refrigerant to be projected through a fine orifice in the cap closure.

One type of closure widely used for this purpose comprises a cork stopper in which is centrally mounted a short length of glass tube, the upper protruding portion of which is drawn out to a taper to provide a fine orifice. The tube contains a small wad of cotton wool to serve as a filter. Stopper and tube are secured in the bottle by an adhesive and are covered by a molded two-part screwcap through a hole in which the glass tube projects. A pivoted spring-biased finger lever is mounted on the screwcap in such a position that one end is pressed on the glass tube orifice and the other extends away from the bottle neck. A small piece of rubber tubing is slipped over the lever end bearing on the orifice and makes a tight seal with it. Finger pressure on the outer lever end frees the orifice and permits a jet of refrigerant to issue.

Another type of closure in use comprises a die-cast screwcap mounted on the bottle with a suitable gasket. The top of the cap is prolonged upwards as a vertical spout in the tip of which a small hole is drilled centrally. A spring-biased finger lever pivotally mounted on the cap serves to control delivery of refrigerant as in the previously described case.

The closures described, while effective for their purpose, have several disadvantages. The use of a cork stopper under the screwcap of the first closure makes refilling and reuse of the dispensing bottle difficult because the adhesive has to be destroyed in order to remove the cork stopper; the fine orifice in the glass tube cannot readily be made with a standard diameter; the number of parts and their assembly on a filled bottle are relatively costly. In the second closure no adequate provision is made for a filter or screen, and the difficulty of drilling a small orifice, say 0.008" in diameter, on a mass production basis in the thick die-cast metal is considerable.

It is an object of my invention to provide a cap closure for a volatile refrigerant container having a jet stream dispensing valve, which is simple and economical to make and assemble, which permits easy refilling of the bottle with refrigerant, which has an accurately reproducible orifice, and which has an interchangeable orifice plate and screen.

For the understanding of my invention, two embodiments are shown in the accompanying drawing and description, but these are intended to be illustrative only,

the scope of my invention being defined in the appended claims.

In the drawing, FIG. 1 is a vertical axis section of one form of my valved closure;

FIG. 2 is a plan view as seen from above;

FIG. 3 is a vertical axial section of another form of my valved closure;

FIG. 4 is a plan view of this closure as seen from above, and

FIG. 5 illustrates the valved closure of FIG. 1 secured on a bottle having an externally threaded neck.

In the embodiment illustrated in FIGS. 1 and 2 a molded plastic cap 1 is provided with an interior female thread 2 adapted to mate with a conventional male thread on a bottle neck. The cap is extended upward axially in a boss 3 provided with an exterior male thread 4 and a central bore 5. Screwed on boss 3 is a smaller molded cap 6 provided with an interior female thread 7, mating with thread 4, and a central bore 8. An annular rubber or similar gasket 9 forms a tight seal between cap 1 and bottle neck.

Between the top of boss 3 and the lower surface of the top of small cap 6 are located an annular rubber or similar washer 10, a disc 11 of bronze screening, and a solid brass disc 12 pierced by a minute central hole 13. The bronze screen 11 may advantageously be of 100 mesh, and the solid disc 12 may be made of 0.010–0.015" thick stock with a central hole 0.008" in diameter. These dimensions, however, may be varied to suit varying conditions of use.

A flat annular metal disc 14 surrounds boss 3 and is secured by cap 6. At one side it has a radial lobe 15 which is struck up in two vertical arms 16, forming a U-shaped support for pivot 17 of finger lever 18. At end 19 of the finger lever a small rubber or similar stopper 20 is inserted friction-tight through hole 21 in a position to bear on and close hole 13. The other end of lever 18 is extended to form a finger piece 22. Spring 23 biases lever 18 in a counterclockwise direction to seal hole 13 unless end 22 of the lever is depressed.

As shown in FIG. 1, the central bore 5 and the central opening in annular washer 10 are of large diameter in comparison with the diameter of "minute central hole" 13 so that the velocity of liquid and vapor passing through the cap is not increased at these points and turbulence is avoided.

In the embodiment illustrated in FIGS. 3 and 4, a sheet metal bottle cap 51 having an internal thread 52 mating with a conventional male thread on a bottle neck (not shown) is provided with a central top opening 55. An annular rubber or similar gasket 59 is located inside cap 51 to form a tight seal with the bottle. Above this is a disc of bronze screening 61 and a solid disc of bronze 62. A second annular washer 59' is located between disc 62 and the under surface of the bottle cap to complete the seal.

As shown in FIG. 3, and as is the case in the previously described embodiment, the central opening in annular washer 59 is of large diameter in comparison with the diameter of "minute hole" 63, so that the velocity of liquid and vapor passing through the cap is not increased at this point, turbulence is avoided and there is no sudden expansion into the protrusion in disc 60.

In both cases, therefore, an unobstructed passage is provided from the interior of the container to and through the foraminous disc and to the delivery hole.

In the center, disc 62 is struck up into a frusto-conical protrusion 60, pierced by a minute hole 63. Thickness of disc 62 and diameter of hole 63 may be in the same range as the corresponding dimensions of disc 12 and hole 13 (FIG. 1).

Secured to the side of cap 51, as by soldering or braz-

ing, is a bracket 66 forming a support for pivot 67 for finger lever 68. The inner end of this lever 69 carries a small rubber stopper 70, mounted friction-tight in hole 71 in a position to bear on and close hole 63. The other end of the lever 68 is extended to form a finger piece 72. Spring 73 biases lever 68 in a counterclockwise direction to seal hole 63 unless end 72 of lever 68 is depressed.

As indicated above, my closure is adapted to serve as a jet stream dispenser when mounted on a conventional bottle of volatile refrigerant used for inducing local anesthesia or analgesia in minor surgical operations. In FIG. 5 one of my closures, as illustrated in section in FIG. 1, is shown mounted on a conventional bottle 101, having a neck 102 provided with an external screw thread 103. Internal screw thread 2 of closure 1 (FIG. 1) mates with thread 103 and serves, on rotation of closure 1 with respect to bottle 101, to seat gasket 9 firmly on upper edge of neck 102. The technique of use is the same as with conventional bottles and refrigerants: the bottle is tipped sufficiently to bring liquid into contact with the closure and the finger piece 22 or 72 is depressed, thus raising stopper 20 or 70 from hole 13 or 63 and permitting a fine stream of refrigerant to issue from the hole; release of the lever closes the hole and shuts off the stream.

My closure has numerous advantages over prior closures. It is readily removed and replaced, thus permitting easy refilling and reuse of the container to which it is attached. It is readily disassembled and reassembled for cleaning and replacement of parts. The pierced disc with minute delivery hole is readily interchangeable so that discs with holes of varying diameters may be used to suit the requirements of the user. Since it is much easier and cheaper to form small holes of a desired diameter to a small tolerance in a thin metal disc than in glass tubing or in relatively thick die cast metal, my closure has the advantages of economy and dimensional constancy. The fine screen used in my closure is superior to the wad of cotton wool hitherto used to remove foreign particles.

It will be clear to those skilled in the art that certain changes can be made in the embodiments of my closure described above without departing from the scope of my invention. For example, the cap material may be of any dimensionably stable plastic or metallic material inert to the volatile refrigerant used; the screen, instead of being of bronze, may be of stainless steel or other inert metal or alloy or of inert synthetic plastic and may be woven or perforated or porous so long as it permits passage of liquid refrigerant and retains solid foreign particles; the disc having the dispensing hole may also be of other inert material than brass or bronze, such as stainless steel, synthetic plastic or the like.

This application is a continuation-in-part of my copending application for Analgesic Composition and Method, Serial No. 568,140, filed February 27, 1956.

I claim:

1. In a valved closure for a volatile refrigerant comprising a screw-threaded container cap, a member provided with a fine delivery hole affixed to the cap and a spring-biased finger-operated valve mounted on the cap and adapted to open or close the delivery hole, the improvement for producing a controlled jet stream from the delivery hole which comprises: a central bore in the cap, a foraminous disc fixed in the cap transverse to the central bore, a thin solid disc in the cap transverse to the central bore fixedly retained between and in contact with the foraminous disc and the interior top surface of the cap, the thin solid disc being provided in a flat portion thereof with a fine delivery hole alined with the central bore of the cap and adapted to be closed by the spring-biased valve, the parts being so arranged as to provide unobstructed passage from the interior of the container to and through the foraminous disc and to the delivery hole, whereby on opening the spring-biased valve fluid may pass through the cap in substantially nonturbulent flow.

2. A closure as defined in claim 1, in which the foraminous screen is a woven wire mesh of inert metal, the disc is of inert metal, and the resilient member is a wire spring.

3. As an article of commerce the combination comprising: a container having an externally threaded neck on which is secured a closure as defined in claim 1.

4. As an article of commerce the combination comprising: a container and closure as defined in claim 3, said container containing a volatile liquid refrigerant adapted for use in inducing local anesthesia or analgesia in minor surgical procedures.

5. In a valved closure for a volatile refrigerant comprising a screw-threaded container cap, a member provided with a fine delivery hole affixed to the cap and a spring-biased finger-operated valve mounted on the cap and adapted to open or close the delivery hole, the improvement for producing a controlled jet stream from the delivery hole which comprises: a molded plastic cap provided with a central bore and an interior screw thread, a boss extending upward from the cap and provided with a central bore and an exterior screw thread, a smaller cap mounted on the boss and provided with a central bore and an interior thread mating with the exterior thread of the boss, an annular washer, a foraminous disc and a thin solid disc provided with a minute central hole retained on top of the boss and within the smaller cap, the washer resting on the boss, the foraminous disc on the washer and the thin solid disc on the foraminous disc, the minute hole in the thin solid disc being accessible to the closing action of the spring-biased valve through the central bore in the smaller cap, whereby an unobstructed passage is provided from the interior of the container to and through the foraminous disc and to the minute hole.

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United States Patent Office 3,813,384 Patented May 28, 1974

3,813,384

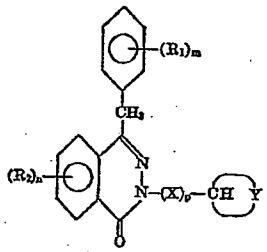
BASICALLY SUBSTITUTED BENZYL PHTHALAZONE DERIVATIVES, ACID SALTS THEREOF AND PROCESS FOR THE PRODUCTION THEREOF

Dietrich Vogelsang, deceased by Ursula Vogelsang Nee Schafer, Heir Helpup, Gerhard Scheffler, Sennei, Norbert Brock, Uerentrup, and Dieter Lenke, Bielefeld, Germany, assignors to Asta-Werke Aktiengesellschaft, Chemische Fabrik, Westfalen, Germany

No Drawing. Filed Jan. 17, 1972, Ser. No. 218,532
Int. Cl. C07d 25/00, 51/06
U.S. Cl. 260—239 A 4 Claims

ABSTRACT OF THE DISCLOSURE

New basically substituted benzyl phthalazone derivatives of formula I



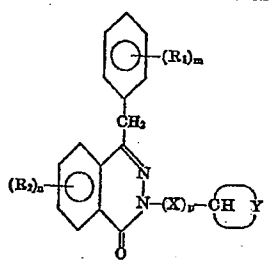
I

and their pharmacologically acceptable acid addition salts thereof. These new benzyl phthalazone derivatives are excellent antihistamines and therefore useful in the treatment of histamine induced disturbances.

The present invention is related to new basically substituted benzyl phthalazone derivatives having a high antihistamine effectiveness, the physiologically acceptable acid addition salts thereof, and process for the production thereof.

The new benzyl phthalazone derivatives according to the present invention are characterized by a cyclic basic residue which is connected with the amide nitrogen atom in the position 2 of the phthalazone nucleus by a carbon atom of this cyclic basic residue directly or by way of an alkylene chain. Basically substituted phthalazones are known already for instance from German patent specification 1,046,625. These phthalazones are compounds having the basic residue substituted on an aliphatic alkylene chain, this basic residue being a tertiary amine substituted by two alkyl groups or by an alkylene group to form a cyclic residue. However, these cyclic basic residues are connected with the amide nitrogen atom of the phthalazone nucleus by the nitrogen atom of the cyclic amine by way of the alkylene chain.

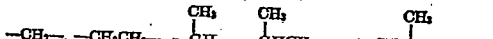
The basically substituted benzyl phthalazone derivatives according to the present invention have the formula I



I

wherein R_1 and R_2, which may be identical or different from each other, represent hydrogen, halogen, lower alkyl,

lower alkoxy, hydroxy, trifluoromethyl, nitro or substituted or unsubstituted amino groups, X is an alkylene group having the formula



m and n, which may be identical or different from each other, represent integers between 1 and 3, p is 0 or 1, and the groupment

represents an unsubstituted monocyclic, bicyclic or tricyclic residue having from 3 to 8 carbon atoms and one or two nitrogen atoms or such a residue being substituted by one or several lower alkyl groups, the nitrogen atom or atoms of this residue being substituted by hydrogen or a lower alkyl group having from 1 to 4 carbon atoms which lower alkyl group may be connected with another atom of the cyclic residue thus forming a bicyclic or tricyclic group.

In view of their particular good properties those compounds of formula I and their physiologically acceptable acid addition salts are preferred wherein R_1 and R_2 represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy or trifluoromethyl, and m and n are 1 or 2. Particularly preferred are those compounds of this preferred group, wherein R_1 represents such a group as indicated above and R_2 is a hydrogen atom.

Among these compounds those benzyl phthalazones and salts are preferred, wherein X is $—CH_2—$ or

Most preferred compounds among the latter group of compounds are those, wherein additionally the groupment

contains 4 to 7 carbon atoms in the cyclic group, in particular the N-substituted pyrrolidinyl, piperidyl, perhydroazepinyl, quinuclidyl, tropanyl and scopyl groups, the tropanyl and the scopyl groups being connected with the amide nitrogen atom of the phthalazone directly by way of a ring carbon atom of this tropanyl or scopyl group, while the pyrrolidinyl, piperidyl, perhydroazepinyl or quinuclidyl residue is connected with the amide nitrogen atom of the phthalazone either directly or by way of an alkylene chain X enumerated hereinabove as preferred.

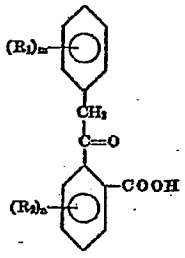
The most preferred group of compounds of Formula I and their physiologically acceptable acid addition salts comprises those compounds wherein R_1 is a hydrogen, fluorine, chlorine or bromine atom or a methoxy, ethoxy, methyl, hydroxy or trifluoromethyl group, R_2 is a hydrogen atom, m is 1 or 2, p is 0, and the groupment

is the N-methyl perhydroazepinyl, the tropanyl or the quinuclidyl group, in particular the N-methyl perhydroazepinyl-(4), the tropanyl-(3) or the quinuclidyl-(3) group. Thus, the annelled benzene ring of these benzyl phthalazone derivatives is unsubstituted and the perhydroazepinyl, tropanyl or quinoclidyl residue is connected directly with the amide nitrogen atom of the phthalazone nucleus.

The process for producing the new, basically substituted benzyl phthalazone derivatives of formula I and the

physiologically acceptable acid addition salts thereof is characterized by that

(A) a compound of formula II

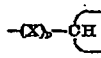


II

or a reactive derivative thereof, wherein R_1, R_2, m and n have the same meaning as in formula I, is subjected to reaction with a hydrazine of formula III

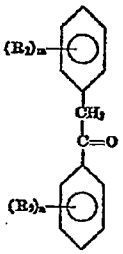
$$H_2N—NH—R_3 \qquad III$$

wherein R_3 is hydrogen or the groupment



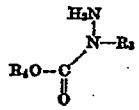
wherein X, p and Y have the same meaning as in formula I, or

(B) a compound of formula IV



IV

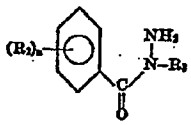
wherein R_1, R_2, m and n have the same meaning as in formula I, is subjected to reaction with a compound of formula V



V

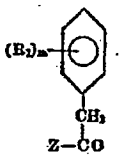
wherein R_3 has the same meaning as in formula III and R_4 is a lower alkyl group, or

(C) a compound of formula VI



VI

wherein R_2 and n have the same meaning as in formula I and R_3 has the same meaning as in formula III, is subjected to reaction with a compound of formula VII



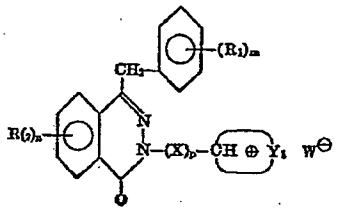
VII

wherein R_1 and m have the same meaning as in formula I and Z is a halogen atom or a hydroxy or alkoxy group, or

(D) a compound of formula I wherein the nitrogen atom of the basic residue

is substituted by hydrogen, is subjected to reaction with an alkylating agent or

(E) a compound of formula IX



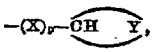
IX

wherein R_1, R_2, m, n, X and p have the same meaning as in formula I and where $W^{\ominus}$ is an anion, is subjected to hydrogenation,

and subjecting a resulting benzyl phthalazone derivative wherein R_3 is hydrogen, to reaction with a compound of formula VIII

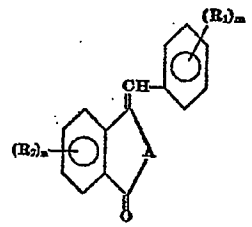
$$Q—R_3 \qquad VIII$$

wherein Q represents an atom or group which upon substitution of the amide nitrogen atom, is split off together with its electron doublet, such as a halogen atom or a sulfonic ester group, and R_3 is the group



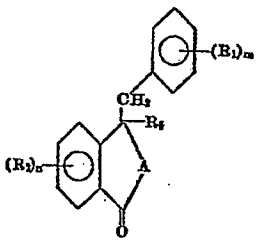
X, p and Y having the same meaning as in formula I, and converting the thus obtained benzyl phthalazone derivatives, if desired, with an appropriate acid into a physiologically acceptable acid addition salt or converting a resulting salt of these benzyl phthalazone derivatives into the free base.

A reactive derivative of the carboxylic acid of formula II is in particular an acid halogenide, ester or anhydride. Other reactive derivatives of the compounds of formula II, which may be used instead of the benzene —o-keto-carboxylic acid or its halogenide, ester or anhydride, are the unsaturated or saturated phthalides or phthalimidines of the formula X



X

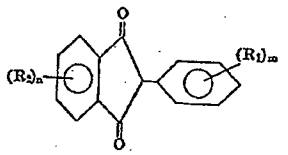
and XI



XI

In the above formulas X and XI, R_1, R_2, m and n have the same meaning as in formula I and A is an oxygen atom or imino group and R_5 is halogen, NH_2, ArNH, OH,

an alkoxy group or the like. Other compounds of this type are those of formula XII



XII

wherein R_1, R_2, m and n have the same meaning as in formula I. These compounds produce derivatives of the benzene-o-ketocarboxylic acid of formula II when subjected to reaction with a compound of formula III.

The above procedures A, B and C are carried out in the absence or presence of usual solvents and auxiliary agents at a temperature elevated up to about 180° C. and in a pH range varying from the acidic to the alkaline pH.

Useful solvents are, for instance, water, alcohols, dimethylformamide, dioxane, pyridine, triethylamine and hydrocarbons. Useful auxiliary agents are bases, acids and condensation agents usual for such reactions.

The procedure D is carried out with usual alkylating agents such as fomaldehyde in the presence of a reducing agent such as formic acid, $NaBH_4$ or hydrogen, as well as dimethylsulfate and K_2CO_3, alkyl halogenides or diazomethane. The reaction E preferably is carried out with catalytic hydogen. Useful catalysts are preferably the precious metal and nickel catalysts.

When carrying out the reaction with the alkylating agents of formula VIII, the known cyclammonium rearrangement may take place with a change in the ring size.

The compounds of formula I and their acid addition salts to a great extent are optically active with the carbon atom of the cyclic base group which is connected with the amide nitrogen atom of the phthalazone nucleus directly or by way of an alkylene group. The racemates may be split up into the optical antipodes in manners known per se.

The compounds according to the present invention are histaminolytically active. They are characterized by an extremely high activity upon parenteral and above all oral application. They furthermore produce this high activity over a long period of time. This activity may be shown in the histamine aerosol test on guinea-pigs or in the lesion test in humans, the lesion being caused by histamine or a histamine liberator (Quaddel-Test).

In guinea-pigs, the histaminolytical activity has been tested in the histamine aerosol test. Guinea-pigs of the Pirbright race and weighing 300 to 700 grams each have been tested. The animals inhale an aerosol of an aqueous solution of histamine dihydrochloride in a concentration of 4 mg./ml. The inhalation produces severe dyspnea (severe shortness of breath, lateral positioning) in untreated animals within 2 minutes. In order to determine the histaminolytical activity, the test compounds are applied subcutaneously or orally to groups of 8 to 10 animals. Thereafter, the test animals are treated for varying times with the histamine aerosol. The test animals are considered as protected if they tolerate the inhalation of the aerosol for 10 minutes without showing severe dyspnea (lateral positioning).

For evaluating the test results, the mean effective doses (DE 50 mg./kg.) are determined by means of a probit analysis from the relation between the dose logarithm and the frequency of protection.

Compounds which are similar in chemical structure to the compounds of the present invention and, therefore, have been used for comparative tests, are 4-benzyl-2-(2-dimethylaminoethyl) - 1 - (2H) - phthalazinone (trade product Ahanon® according to German patent specification No. 1,046,625; compound A in Tables I and II) and β - dimethylaminoethyl - (4-chloro-α-methylbenzhydryl)-ether known as highly active histaminolytic (generic

name: chlorophenoxamine; H. Arnold et al., Arzneim.-Forsch, *4*, 189 (1954); N. Brock et al., Arzneim.-Forsch. *4*, 262 (1954); compound B in Tables I and II).

The difference between the products according to the present invention and the comparative products A and B is particularly obvious when administering the test compounds to the test animals orally and treating the test animals with the histamine aerosol 8 hours later. Upon application of 0.0215 mg./kg. of 4-(p-fluorobenzyl)-2-[N-methyl-perhydroazepinyl-(4)]-1-(2H) - phthalazinone or 0.215 mg./kg. of 4 - (p - chlorobenzyl) - 2-[N-methyl-perhydroazepinyl-(4)]-1 - (2H) - phthalazino or 4-(p-chlorobenzyl) - 2-[quinclidyl-(3)]-1-(2H)-phthalazinone not one of the 8 to 10 animals of each group showed dyspena with lateral positioning after treatment with the histamine aerosol. In striking contract thereto, upon applictaion of 10 to 100 times the dose of both comparative compounds (2.15 mg./kg.) 9 of 10 aminals with compound A and 10 of 10 animals with compound *b* still showed very severe dyspnea with lateral positioning.

TABLE I

Histaminolytical activity in the histamine aerosol test on guinea-pigs; subcutaneous administration of test compounds 1 hour before treatment with the aerosol

Example number	DE 50 (mg./kg.)	Relative activity [1]
3	0.0062	17.7
6	0.011	10.0
7	0.0071	15.5
9	0.045	2.44
10	0.031	3.55
11	0.035	3.14
12	0.022	5.00
19	0.016	6.88
24	0.027	4.07
28	0.059	1.86
30	0.026	4.23
33	0.016	6.88
34	0.019	5.79
A	0.11	1.00
B	0.11	1.00

[1] Activity of A=1.00.

TABLE II

Histaminolytical activity in the histamine aerosol test on guinea-pigs; oral administration of test compounds 2 and 8 hours before treatment with the aerosol

Example number	DE 50 (mg./kg.)		Relative activity [1]	
	2 hours	8 hours	2 hours	8 hours
9	0.16	0.49	19.4	18.1
10	0.037	0.029	83.8	221
19	0.010	0.011	310	582
24	0.087	0.052	35.6	123
28	0.20	0.28	15.5	22.9
30	0.038	0.35	81.6	18.3
A	3.1	6.4	1.00	1.00
B	0.52	6.2	5.96	1.03

[1] Activity of A 3 1.00.

The histaminolytical activity of the compounds according to the present invention is substantially higher than those of the comparative test compounds A and B. Upon subcutaneous administration, the relative activity is about 17.7 times larger (Example No. 3) than that of the comparative test compounds. The activity is particularly evident upon oral administration (Table II). The activity is 16 to 310 times higher in a 2 hours test in comparison to the activity of test compound A and is 13 to 582 times higher in the 8 hours test. The 8 hours test clearly demonstrates the very high oral activity of the compounds according to the present process which activity is produced over a prolonged period of time.

The compounds according to the present invention are used as active ingredients in pharmaceutical preparations and may be administered in usual embodiments such as tablets, dragees, capsules, suppositories, drops, ointments, creams as well as injection solutions. They are in particular used for the treatment of the various forms of allergies. Thus, they have been used successfully in humans in the treatment of asthma bronchiale, for the treatment of disorders of the skin and mucous membranes such as urticaria, Quincke's edema, pruritus, eczemas,

hay fever and rhinitis vasmotorica. In general, they are administered in such treatments in a dosage of 0.4 to 4 mg. per day and human patient. The symptoms of the above allergic diseases may be effectively reduced upon a single dose for up to 24 hours. The effectiveness of the compounds of the present invention in humans which is produced very rapidly and over a prolonged period of time in comparison to other antihistamines, may be particularly well shown in the reduction of the size of an artificially produced lesion by means of a histamine liberator according to L. Kerp, H. Kasimiar, P. N. Tie, Med. Welt 17 NF, 2794 (1966). The compounds according to the present invention may be used as such or in combination with other active ingredients as they are usual in antihistaminic preparations. With this respect their minimal dose is most advantageous.

The present invention is further illustrated by the following examples. The constitution of the final products has been verified by elementary analysis and infrared and NMR spectra.

EXAMPLE 1

4-benzyl-2-[N-methylpyrrolidinyl-(3)-methyl]-1-(2H)-phthalazinone

10.3 g. of phenylacetophenone-o-carboxylic acid and 6.1 g. of hydrazine sulfate are dissolved in a solution of 3.6 g. of NaOH in 100 cc. of water. The solution is heated to boiling for 2 hours. The precipitate is filtered off with suction, washed with water and dried. The thus obtained 9.2 g. of 4-benzyl-1-(2H)-phthalazinone are added to a solution of 1.4 g. of metallic potassium in 250 cc. of anhydrous alcohol. The resulting mixture is heated to boiling for 30 minutes. The alcohol is distilled off. 10.6 g. of the potassium salt are obtained.

12.4 g. of the tosyl ester of 3-hydroxymethyl-N-methylpyrrolidine and 10.6 g. of the sodium salt of 4-benzyl-1-(2H)-phthalazinone in 100 cc. of dimethylformamide are heated for one hour at 100° C. The solvent is separated in a rotary evaporator and the residue is triturated with water. The insolubles are dissolved in ether and the ethereal solutions are extracted with dilute hydrochloric acid. The acidic extracts are rendered alkaline by the addition of an aqueous potassium hydroxide solution. The separated oily product is dissolved in ether and the ethereal solutions are dried over anhydrous Na_2SO_4. Upon evaporation of the ether, 11 g. of the base are obtained. The fumarate crystallizes as monohydrate. F.p.: 129–132° C.

EXAMPLE 2

4-benzyl-2-{2-N-methylpiperidyl-(2)]ethyl}-1-(2H)-phthalazinone

13.3 g. of phenylacetophenone-o-carboxylic acid and 7.9 g. of hydrazine sulfate are heated with 4.7 g. of NaOH in 150 cc. of water. 11.9 g. of 4-benzyl-1-(2H)-phthalazinone are recovered as described in Example 1. This compound is subjected to reaction with a solution of 1.9 g. of metallic potassium in 300 cc. of anhydrous alcohol as described in Example 1, thus resulting in 13.7 g. of the potassium salt of 4-benzyl-1-(2H)-phthalazinone.

A solution of 8.9 g. of 2-(2-chloroethyl) - N - methyl piperidine in 25 cc. of dimethylformamide are added dropwise at 100° C. to a solution of 13.7 g. of the potassium salt of 4-benzyl-1-(2H)-phthalazinone in 150 cc. of dimethylformamide. The resulting solution is further stirred for 2 hours. The solvent is distilled off and the residue is treated with water. The insoluble product is dissolved in ether, the ethereal solutions are extracted with dilute hydrochloric acid and the acidic extracts are rendered alkaline by the addition of aqueous potassium hydroxide with cooling. The separated oil is again dissolved in ether and the ethereal solution is dried over anhydrous Na_2SO_4. The hydrochloride of 4-benzyl-2-{2-[N-methylpiperidyl (2)] - ethyl} - 1 - (2H) - phthalazinone is precipitated by dropwise addition of ethereal hydrochloric acid. Thus, 14 g. of the hydrochloride are obtained. After recrystallization, the hydrochloride melts at 201–203° C.

The following compounds have ben prepared as described in Examples 1 and 2:

(3) 4 - (p - chlorobenzyl) - 2 - [N-methylpyrrolidinyl-(2)-methyl] - 1 - (2H) - phthalazinone hydrochloride. F.p.: 206–207° C.

(4) 4-(p - chlorobenzyl) - 2 - [N - methylpiperidyl)-(2) - methyl] - 1 - (2H)-phthalazinone sulfate hydrate. F.p.: above 90° C. (with decomposition).

(5) 4-benzyl - 2 - [N - methylpiperidyl - (3) - methyl]-1 - (2H) - phthalazinone hydrochloride hydrate. F.p.: above 77° C. (with decomposition).

(6) 4-(p - methylbenzyl) - 2 - [N - methylpyrrolidinyl-(2)-methyl] - 1 - (2H) - phthalazinone hydrochloride hydrate. F.p. 126–128° C.

(7) 4-(p - methoxybenzyl - 2 - [N - methylpyrrolidinyl-(2) - methyl] - 1 - (2H) - phthalazinone. F.p.: 111–114° C.

(8) 4-(p - chlorobenzyl) - 2 - {1 - [N-methylpiperidyl-(2)] - ethyl} - 1 - (2H) - phthalazinone citrate. F.p.: 103–105° C.

EXAMPLE 9

4-benzyl-2-[N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone

A solution of 8 g. of 4-chloro-N-methyl-perhydroazepine in 20 cc. of toluene are added to a suspension of 13.7 g. of the potassium salt of 4-benzyl-1-(2H)-phthalazinone in 250 cc. of anhydrous toluene dropwise with vigorous stirring at 40° C. Heating is continued slowly to boiling whereafter refluxing is continued for another 5 hours. The solvent is separated in a rotary evaporator and the residue is washed with water. The insoluble oily product is dissolved in ether and the ethereal solution is extracted with dilute hydrochloric acid. The acidic extracts are rendered alkaline by the addition of aqueous potassium hydroxide and the separated oil is again dissolved in ether. The ethereal solutions are dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, 32 g. of a raw product are obtained. This product is converted into the fumarate which is recrystallized, thus resulting in the fumarate hydrate of the 4-benzyl-2-[N-methyl-perhydroazepinyl - (4)] - 1 -(2H) - phthalazinone. F.p.: 156–160° C.

In addition, 4-benzyl-2-{2-[N-methyl-pyrrolidinyl-(2)] ethyl}-1-(2H)-phthalazinone may be recovered from the mother liquors.

EXAMPLE 10

4-(p-chlorobenzyl)-1-[N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone

30.6 g. of p-chlorobenzylacetophenone - o - carboxylic acid and 16 g. of hydrazine sulfate are heated with 9.4 g. of NaOH in 250 cc. of water. After washing and drying, 27 g. of 4-(p-chlorobenzyl)-1-(2H)-phthalazinone are obtained.

20 g. of 2-(2-chloroethyl)-N-methylpyrrolidine hydrochloride are added to a solution of 4.4 g. of NaOH in 20 cc. of water. This solution is heated to 70° C. and added dropwise to a mixture of the above obtained 27 g. of 4-(p-chlorobenzyl)-1-(2H)-phthalazinone and 40 cc. of 50% soda lye heated to 70° C. The mixture is kept at this temperature and heated for another hour. After cooling and diluting with water, the insoluble materials are separated and dissolved in methylene chloride. The solution is extracted with dilute hydrochloric acid and the acidic extracts are rendered alkaline by the addition of aqueous potassium hydroxide. The separated oil is again dissolved in methylene chloride and the solution is dried and evaporated. The crude final product is obtained in a yield above 90% of the theoretical. It is converted into a salt and purified by recrystallization. The hydrochloride of 4-(p - chlorobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)] - 1 (2H) - phthalazinone melts at 225–229° C.

4-(p-chlorobenzyl)-2-{2-[N - methylpyrrolidinyl-(2)]-ethyl}-1-(2H)-phthalazinone may be recovered from the filtrate from recrystallization.

The following compounds have been prepared as described in Examples 9 and 10.

(11) 4-(p-methylbenzyl) - 2-[N - methyl-perhydroazepiny l -(4)]-1-(2H)-phthalazinone sulfate. F.p.: 199–203° C.

(12) 4-(p-methoxybenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone sulfate. F.p.: 203–205° C.

(13) 4-(3,4 - dimethoxybenzyl) - 2-[N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone sulfate. F.p.: 118–120° C.

(14) 4-(2-chlorobenzyl-2 - [N-methyl-perhydroazepinyl (4)]-1-(2H) - phthalazinone hydrochloride. F.p.: 198–200° C.

(15) 4-(3-chlorobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone. F.p.: 77–78° C.

(16) 4-(p-chlorobenzyl)-6,7 - dimethoxy-2-[N-methyl-perhydroazepinyl-(4)]-1 - (2H)-phthalazinone sulfate. F.p.: 286–290° C.

(17) 4-(2,4-dichlorobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone fumarate. F.p. 207–211° C.

(18) 4-(p-dimethylaminobenzyl)-2-[N - methyl-perhydroazepinyl-(4)]-1 - (2H)-phthalazinone fumarate. F.p.: 177–182° C.

(19) 4-(p-fluorobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone sulfate. F.p.: 211–220° C.

(20) 4-(p-bromobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone sulfate. F.p.: 215–220° C.

(21) 4-(p-acetaminobenzyl)- 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone hydrochloride hydrate. F.p. 275–278° C.

(22) 4-(p-aminobenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone dihydrochloride hydrate. F.p. 270–277° C.

(23) 4-(p-hydroxybenzyl) - 2 - [N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone hydrochloride hydrate. F.p.: 260–266° C.

EXAMPLE 24

4-(p-chlorobenzyl)-2-[quinuclidyl-(3)]-1-(2H)-phthalazinone

5.5 g. of p-chlorophenylacetophenone-o-carboxylic acid are dissolved in 30 cc. of 2 N soda lye and 30 cc. of water. 4.3 g. of 3-quinuclidyl-hydrazine dihydrochloride are added thereto and the mixture is heated to boiling for 3 hours under an atmosphere of nitrogen. Upon cooling, a highly viscous red oil is separated which crystallizes upon scratching. The solid material is filtered off, washed with water and recrystallized, 4.4 g. of 4-(p-chlorobenzyl)-2-[quinuclidyl-(3)] - 1 - (2H)-phthalazinone are obtained. This product melts at 181–182° C.

EXAMPLE 25

4-(p-chlorobenzyl)-2-[N-methylpiperidyl-(4)]-1-(2H)-phthalazinone

11 g. of p-chlorophenylacetophenone-o-carboxylic acid are dissolved in 120 cc. of ethyl alcohol. A solution of 8 g. of N-methylpiperidyl-(4)-hydrazine dihydrochloride are added thereto and the mixture is heated to boiling for 8 hours under an atmosphere of nitrogen. The alcohol is distilled off and the residue is triturated with dilute soda lye. The insoluble oily product is dissolved in chloroform, the chloroform solution is washed and dried. Upon evaporation, 8.4 g. of the phthalazinone base are obtained. The fumarate melts at 191–193° C.

The following compounds have been prepared as described in Examples 24 and 25.

(26) 4-benzyl - 2 - [N-methylpiperidyl-(4)]-1-(2H)-phthalazinone hydrate. F.p.: 106–110° C.

(27) 4-(p-chlorobenzyl) - 2 - [1,3-dimethyl-piperidyl-(4)]-1-(2H)-phthalazinone fumarate. F.p.: 219–221° C.

(28) 4-(p-chlorobenzyl) - 2 - [tropanyl-(3)]-1-(2H)-phthalazinone hydrochloride hydrate. F.p.: 270–274° C.

(29) 4-benzyl - 2 - {2 - [N-methylpyrrolidinyl-(2)]-ethyl}-1-(2H)-phthalazinone fumarate hydrate. F.p.: 95–99° C.

(30) 4-benzyl-2-[quinuclidyl-(3)] - 1 - (2H)-phthalazinone fumarate hydrate. F.p.: 233–235° C.

(31) 4 - (p-chlorobenzyl)-2 - {2-[N-methylpyrorolidinyl-(2)]-ethyl} - 1 - (2H)-phthalazinone hydrochloride. F.p.: 220–224° C.

(32) 4 - (p-chlorobenzyl)-2 - [N - methylpyrrolidinyl-(3)]-1-(2H)-phthalazinone. F.p.: 117–120° C.

(33) 4-(p-methoxybenzyl) - 2 - [quinuclidyl-(3)]-1-(2H)-phthalazinone hydrochloride. F.p.: 236–237° C.

(34) 4-(p-fluorobenzyl) - 2 - [N-methylpyrrolidinyl-(3)]-1-(2H)-phthalazinone. F.p.: 90–93° C.

(35) 4 - (p-methylbenzyl) - 2-[N - methylpyrrolidinyl-(3)]-1-(2H)-phthalazinone. F.p.: 96–98° C.

(36) 4-(p-chlorobenzyl) - 2 - [nortropanyl-(3)]-1-(2H)-phthalazinone hydrochloride. F.p.: 320° C.

(37) 4 - (p - chlorobenzyl) - 2 - [perhydroazepinyl-(4)]-1-(2H)-phthalazinone fumarate, F.p.: decomposition.

EXAMPLE 38

4-(p-chlorobenzyl)-2-[N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone

1.0 g. of 4-(p-chlorobenzyl)-2-[perhydroazepinyl-(4)]-1-(2H)-phthalazinone are heated to boiling for 5 hours with 10 g. of a 40% aqueous formaldehyde solution and 11.6 g. of formic acid. The solution is evaporated and the residue is triturated with dilute soda lye. The insoluble material is dissolved in chloroform and the chloroform solution is dried and evaporated. The residue is dissolved in ether. 0.8 g. of the hydrochloride are precipitated by the addition of etheral hydrochloric acid. After recrystallization from alcohol, the compound melts at 225–229° C. This compound is identical with the final product obtained according to Example 10.

The following compound has been prepared as described in Example 38:

(39) 2 - [N-methyl-perhydroazepinyl - (4)] - 4 - (p-trifluoromethylbenzyl)-1-(2H)-phthalazinone.

EXAMPLE 40

4-(p-chlorobenzyl)-2-[N-methylpiperidyl-(3)]-1-(2H)-phthalazinone

4.9 g. of 3 - [4 - (p-chlorobenzyl)-1-oxo-phthalazinyl-(2)]-1-methylpyridinium iodide are subjected to hydrogenation in 300 cc. of ethyl alcohol in the presence of PtO_2 as catalyst for 7 hours at 80° C. and at a hydrogen pressure of 100 atmospheres. The catalyst is filtered off and the alcohol is distilled off. The residue is treated with dilute soda lye and the insoluble materials are dissolved in methylene chloride. The methylene chloride solution is washed with water and dried over potash. The solvent is filtered off and the solid residue is recrystallized from 60 to 70% ethyl alcohol. The yield is 2.5 g. F.p.: 154–156° C.

The following compounds have been prepared as described in Example 40:

(41) 4 - (p-methylbenzyl) - 2 - [N-methylpiperidyl-(3)]-1-(2H)-phthalazinone. F.p.: 137–139° C.

(42) 4 - (p-methoxybenzyl) - 2 - [N-methylpiperidyl-(3)]-1-(2H)-phthalazinone. F.p.: 87–93° C.

EXAMPLE 43

Tablets containing the products according to the present invention are prepared according to the following recipe as exemplified with the compound of Example 19:

	Mg.
Active ingredient according to Example 19	1.0
Corn starch	51.0
Secondary calcium phosphate, anhydrous	20.0
Lactose	20.0
Polyvinylpyrrolidone	3.0
Talcum	4.0
Magnesium stearate	1.0
	100.0

The active compound is dissolved together with the polyvinylpyrrolidone in 5 times the amount of chloroform. A homogeneous mixture of calcium phosphate, lactose and 60% of the corn starch are mixed therewith and granulated. The dried granulate sieved to a maximal particle size of 0.75 mm. is mixed with the remaining amount of corn starch, talcum and magnesium stearate for half an hour and the mixture is pressed to tablets weighing 100 mg. each and having a diameter of 6 mm.

EXAMPLE 44

As described in Example 43, dragee-kernels weighing 100 mg. having a diameter of 6 mm. and a camber diameter of 5 mm. are prepared. These kernels are coated with a usual dragee coating to a final weight of 170 mg.

Another batch of kernels is sprayed with a lacquer solution instead of the dragee coating. The resulting lacquer coating comprises:

	Mg.
Hydroxypropylmethyl cellulose	1.6
Ethyl cellulose	0.5
Polyglycol 4000	0.4
1,2-propylene glycol	0.25
Titanium dioxide	0.25

The above recipes of the Examples 43 and 44 may be further followed by using a smaller amount of the active ingredient, such as 0.6 and 0.3 mg. instead of 1 mg. The difference in weight is balanced by additional amounts of corn starch.

EXAMPLE 45

1 g. of the hydrochloride of active ingredient of Example 10 are milled to a particle size of less than 75μ. The resulting product is mixed slowly with 999 g. of molten suppository fat at 40° C. with vivid stirring. The homogeneous mixture is poured into suppository molds to give suppositories weighing each 1.0 g. In an analogous manner, suppositories may be prepared containing 0.5 mg., 2 mg. or 6 mg. of active ingredient.

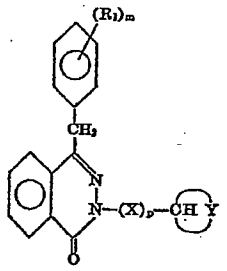
EXAMPLE 46

300 mg. of the active compound of Example 19 as hydrochloride are dissolved together with 855 mg. of sodium chloride in 90 cc. of water for ampoules and the

solution is filled up to 100 cc. The resulting solution is thoroughly filtered and filled into ampoules measuring 1.1 cc. each. The closed ampoules are sterilized in an autoclave with steam under pressure at at least 120° C. for half an hour.

What we claim is:

1. A benzyl phthalazone compound of the Formula



wherein R_1 is a member selected from the group consisting of hydrogen, fluorine, chlorine, bromine, methoxy, ethoxy, methyl, hydroxy and trifluoromethyl, X is a member selected from the group consisting of $-CH_2-$ and $-CH(CH_3)-$, m is 1 or 2, p is 0 or 1 and

is N-methyl perhydroazepinyl and the physiologically acceptable acid addition salts of said phthalazone derivative.

2. A benzyl phthalazone compound according to claim 1 wherein p is 0 and the physiologically acceptable acid addition salts of said phthalazone derivative.

3. 4 - (p-fluorobenzyl)-2-[N-methyl-perhydroazepinyl-(4)]-1-(2H)-phthalazinone and the pharmacologically acceptable acid addition salts thereof.

4. 4-(p-chlorobenzyl)-2-[N - methyl-perhydroazepinyl-(4)] - 1 - (2H)-phthalazinone and the pharmacologically acceptable acid addition salts thereof.

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260—250, 293.87, 292; 424—244, 250

United States Patent [19]

Engel et al.

[11] **Patent Number: 4,704,387**

[45] **Date of Patent: Nov. 3, 1987**

[54] **N-BENZYL, PHENETHYL, METHOXYETHYL OR ALLYL SUBSTITUTED BENZYLPHTHALAZINONES HAVING ANTIALLERGIC AND ANTIHISTAMINE ACTION**

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[73] Assignee: **ASTA-Werke Aktiengesellschaft, Chemische Fabrik, Bielefeld, Fed. Rep. of Germany**

[21] Appl. No.: **764,995**

[22] Filed: **Aug. 12, 1985**

[30] **Foreign Application Priority Data**

Sep. 14, 1984 [DE] Fed. Rep. of Germany 3433776

[51] **Int. Cl.**[4] **A61K 31/55; C07D 403/04; C07D 223/12; C07D 237/32**

[52] **U.S. Cl.** **514/212; 540/598; 544/357**

[58] **Field of Search** 544/357; 260/243.3; 514/212; 540/598

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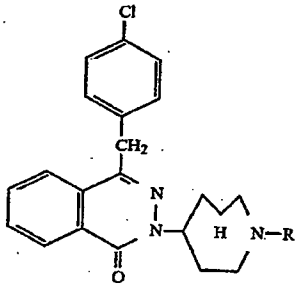
[57] **ABSTRACT**

Compounds of the formula



I

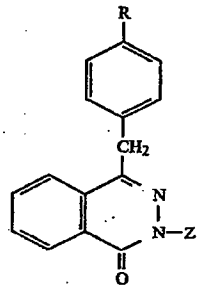
wherein R is a benzyl group, a phenylethyl group, a methoxyethyl group or an allyl group having an antiallergic activity.

11 Claims, No Drawings

N-BENZYL, PHENETHYL, METHOXYETHYL OR ALLYL SUBSTITUTED BENZYLPHTHALAZINONES HAVING ANTIALLERGIC AND ANTIHISTAMINE ACTION

BACKGROUND OF THE INVENTION

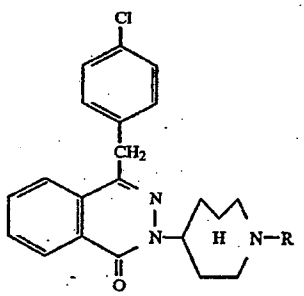
German Pat. No. 2164058 is directed to basic substituted 4-benzyl-1-(2H)-phthalazinone derivatives of the following formula



wherein R is a hydrogen or halogen atom, a trifluoromethyl group, or a lower alkyl or alkoxy group and Z is a 4-perhydroazepinyl, N-methyl-4-perhydroazepinyl, 3-quinuclidyl, 3-tropanyl, 3-nortropanyl, N-methyl-3-pyrrolidinyl or N-methyl-2-pyrrolidinyl-methyl group, as well as the physiologically compatible acid addition salt. These compounds have an antihistamine action.

SUMMARY OF THE INVENTION

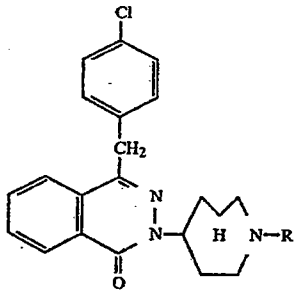
The invention is directed to substituted benzylphthalazinone derivatives of the formula



I

wherein R is a benzyl group, a phenylethyl group, a methoxyethyl group or an allyl group or a physiologically compatible acid addition salt thereof.

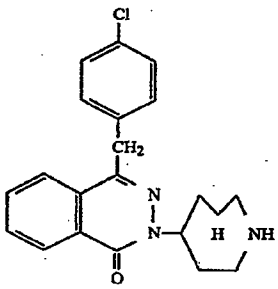
There is also included a process for the production of a substituted benzylphthalazinone derivative of the formula



I

wherein R is a benzyl group, a phenylethyl group, a methoxyethyl group or an allyl group or a physiologically compatible acid addition salt thereof comprising:

(a) reacting a compound of the formula



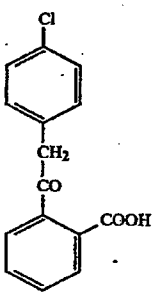
II

with a compound of the formula

III

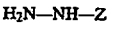
wherein R is defined as in formula I and X is a hydroxy group esterified with a strong inorganic or organic acid or

(b) a compound of the formula



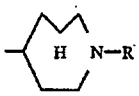
IV

or a reactable derivative thereof is reacted with a hydrazine of the general formula:

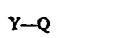


V

wherein Z is hydrogen or the group

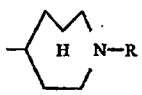


and R is as defined in formula I, with the proviso that where Z is hydrogen the benzyl-phthalazinone derivative obtained is subsequently reacted with a compound of the formula:

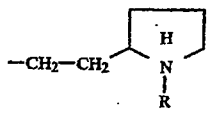


VI

wherein Y is a halogen atom, e.g. chlorine, bromine or iodine, or a sulfonic acid ester group, e.g. the methyl or ethyl ester, and Q is either the group



or the group



and R is as previously defined, and optionally the compound obtained is converted into its acid addition salt.

The invention is also directed to the use of the compounds of formula I as therapeutically active materials.

Also the invention is directed to medicines containing a compound of formula I in addition to a customary carrier and/or diluent and/or adjuvant.

The invention also includes a process for the production of a medicine comprising working a compound of general formula I with a customary carrier and/or diluent or other adjuvant to a pharmaceutical preparation or bringing it into a therapeutically usable form.

Finally the invention also includes the use of the compounds of general formula I for the production of medicines.

The compounds of the invention are antiallergic and asthma prophylactically active, however, considerably stronger and better than the known compounds of German Pat. No. 2164058. Furthermore, in contrast to the known medicine AZELASTIN (compound according to Example 5 of German Pat. No. 2164058) they have either no, or a considerably less, bitter taste, so that they can be applied for example even as an aerosol.

In regard to process (a)

The process can be carried out without additional solvent or in a suitable solvent or dispersing agent. As solvent or dispersing agent for example there are included: aromatic hydrocarbons such as for example benzene, mesitylene, toluene, xylene, pyridine, lower aliphatic ketones such as for example acetone, methyl ethyl ketone, halogenated hydrocarbons such as for example chloroform, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene, methylene chloride, ethers such as for example tetrahydrofurane, dioxane, diisopropyl ether, sulfoxides such as for example, dimethylsulfoxide, tertiary acid amides such as for example dimethyl formamide, dimethyl acetamide, hexamethyl phosphoric acid triamide, tetramethylurea, N-methyl pyrrolidone, lower alcohols such as for example methanol, ethanol, isopropanol, amyl alcohol, butanol, tert.butanol as well as mixtures of the agents mentioned. The reaction is carried out for example at temperatures between 20° to 200° C., preferably 40° to 160° C. or even 50° to 120° C. If a solvent or dispersing agent is used, frequently one operates at the reflux temperature of the agent. The reaction frequently runs even at room temperature, or at a temperature between 40° to 120° C.

The reaction is advantageously carried out in the presence of acid binding agents such as alkali carbonates, e.g. sodium carbonate or potassium carbonates, alkali acetates, e.g. sodium acetate or potassium acetate, alkali hydroxides, e.g. sodium hydroxide or potassium hydroxide or tertiary bases (triethylamine, pyridine).

In the event that X is an esterified hydroxyl group then it is a matter of a reactable ester. A reactable ester thereby for example is one of a strong organic or inorganic acid, such as above all, a hydrogen halide, for example hydrochloric acid, hydrobromic acid, hydroiodic acid, or a sulfonic acid,, such as an aryl or C_1–C_6-alkylsulfonic acid, for example lower alkybenzenesulfonic acids (p-toluenesulfonic acid). As solvents there are especially considered agents such as dioxane/ water, dimethylformamide/water or lower saturated aliphatic alcohols, e.g. those mentioned above.

Unknown starting materials of Formula III can be obtained for example analogous, Houben-Weyl, Methoden der Organischen Chemie, Volume 5/3 (1962), page 503 et seq., Volume 6/2 (1963) page 475 et. seq or Volume 9 (1955) page 426.

In regard to (b)

As derivatives of the carboxylic acids of general formula IV which are capable of reaction there are especially considered acid halides (chloride, bromide, iodide), esters (especially with C_1–C_6-alkanols) and anhydrides (for example p-chloro-benzylidene phthalide). The reaction is carried out in the presence or absence of the customary solvents and assistants at temperatures between 40° and 200° C. and in a wide pH range from acid to alkaline.

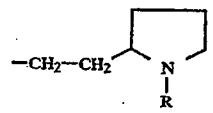
As solvents there are suited for example, water, aromatic hydrocarbons such as for example benzene, mesitylene, toluene, xylene, halogenated hydrocarbons such as for example chloroform, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene, methylene chloride, ethers such as for example tetrahydrofurane, dioxane, diisopropyl ether, sulfoxide such as for example dimethyl sulfoxide, tertiary acid amides such as for example dimethyl-formamide, dimethyl-acetamide, hexamethyl-phosphoric acid, triamide, tetramethyl-urea, urea, N-methyl pyrrolidone; lower alcohols such as for example methanol, ethanol, isopropanol, amyl-alcohol, butanol, tert.butanol and mixtures of the agents mentioned as well as also tertiary amines, for example pyridine. As assistants there can be employed bases, acids and condensation agents conventional for these reactions.

For the reaction of those benzyl-phthalazinone derivatives which are obtained if Z of formula V is hydrogen with a compound Y-Q likewise there are employed the above-mentioned solvents as well as the above-mentioned temperature range.

Especially there are employed as solvent tertiary and amides (for example dimethyl-formamides), aromatic hydrocarbons (for example toluene or even water, whereby frequently the operation is carried out in the presence of basic material (for example alkali hydroxides). Preferably operation is at temperatures between 80°–200° C., especially 80°–150° C.

In the event Y of formula VI is a halogen atom it is chloride, bromine or iodine. In the event Y of formula VI represents a sulfonic acid ester group, it is for example a C_1-C_6-alkylsulfonic acid group (for example CH_3—SO_2—O— an arylsulfonic acid group, such as for example the radical of a C_1-C_4-alkylbenzenesulfonic acid (for example a p-toluenesulfonyloxy group).

The benzyl-phthalazinone starting compound (compounds of formula I where there is a hydrogen atom located on the acidamide nitrogen atom in place of the seven member ring having the substituents) for example is also employed in the form of its alkali salt (Na/K). This type of alkali salt can be obtained for example in customary manner from the corresponding phthalazinone and the alkali metal in alcoholic solution (for example ethanol) or in another customary agent for this at 60° to 100° C. The end products obtained by the reaction with compounds of formula VI in a given case represent at times mixtures of compounds of formula I (having the 7 member ring) and the corresponding compounds which in place of the 7 member ring contain the group



(cycloammonium rearrangement with change of size of the ring. The isolation of the sought for compound I and of the 5 member ring compound for example can be carried out in customary manner by fractional crystallization.

Depending on the process condition and starting materials there is obtained the end product of formula I in free form or in the form of its salt. The salt of the end product can again be converted into the base in known manner, for example with alkali or ion exchangers. From the latter (free base) salts can be obtained by reaction with organic or inorganic acids, especially those which are suited for the formation of therapeutically usable salts, e.g. hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, maleic acid, p-toluenesulfonic acid.

The compounds of the invention of formula I contain an asymmetric carbon atom (C-atom of the 7 member ring which is connected with the acid amide nitrogen atom of the phthalazinone) and therefore as a rule are obtained as the racemate. Such racemates can be resolved into the optically active isomers in known manner for example by fractional crystallization of the salts of a racemic compound I with optically active acids or also by chromatographic separation of the racematic (see for example Angewandte Chemie 92/1 (1980), page 14). However, it is also possible to initially employ an optically active starting material in which case then as end product there is obtained a corresponding optically active form.

The present invention thus includes both the racemate and the corresponding optically active dextro and laevo rotating forms.

The compounds of the invention are suitable for the production of pharmaceutical compositions or preparations. The pharmaceutical compositions or medicines contain as active material one or more of the compounds of the invention, optionally in admixture with other pharmacologically or pharmaceutically active materials. The production of the medicines can be carried out with use of known and customary pharmaceutical carriers and adjuvants.

The compositions can comprise, consist essentially of, or consist of the stated materials and the processes can comprise, consist essentially of, or consist of the steps set forth with the recited materials.

DETAILED DESCRIPTION

EXAMPLE 1

4-(4-chlorobenzyl)-2-(hexahydro-1-benzyl-azepin-4-yl)-1-(2H)-phthalazinone (formula I, R=benzyl)

There were dropped into a mixture of 6 grams (0.013 mole) of 4-(4-chlorobenzyl)-2-(hexahydro azepin-4-yl)-1 (2H)-phthalazinone×HBr in 60 ml of dioxane heated to 50° C., 3.2 grams (0.031 mole=4.4 ml) of triethylamine and subsequently 1.7 grams (0.013 mole=1.5 ml) of benzyl chloride with stirring. After the end of the addition the reaction mixture was stirred for 5 hours at 90° C. After cooling the precipitated ammonium salt was filtered off with suction. The reaction solution was thereupon concentrated to dryness in a vacuum. The residue was recrystallized twice from isopropanol: crystals of M.P. 140°–141° C. Yield: 3.1 grams (51%).

The starting material is obtained for example as follows:

60 grams (0.157 mole) of 4-(p- chlorobenzyl)-2-(hexahydroxy-1-methyl azepin-4-yl)- 1-(2H)-phthalazinone were dissolved with heating to 95° C. in 600 ml of dried toluene. Subsequently there were dropped in with stirring 51.1 grams (0.471 mole=45 ml) of ethyl chloroformate in 45 ml of toluene. The mixture was stirred for 5 hours at 95° C. After cooling to room temperature the reaction mixture was filtered off with suction from the insolubles and concentrated on a rotary evaporator. There remained an oily residue which triturated with a little ether precipitated as a white crystalline product and melted at 103° to 105° C. (Yield: 53.4 grams (77%).

53.4 grams (0.12 mole) of the thus obtained 1-carboxyethyl derivative (formula I, R=$COOC_2H_5$) and 114 ml of a 40% solution of hydrogen bromide in glacial acetic acid heated at 85°–90° C. for 4 hours with intensive stirring, with increasing heating the carboxyethyl compound went into solution. After cooling the solution was concentrated in a vacuum. There was obtained from the viscous, oily residue by recrystallization from methanol the starting compound of formula I, wherein R is hydrogen, in the form of the white, crystalline hydrobromide. The mixture was filtered off with suction, washed several times with methanol and dried in a vacuum, M.P. 138°–140° C. Yield: 51 grams (95%).

EXAMPLE 2

4-(4-Chlorobenzyl)-2-(hexahydro-1

phenethyl-azepin-4 yl)-1-(2H)-phthalazinone (formula I, R=phenylethyl)

There was present a solution of 7 grams (0.015 mole) of 4- (4-chlorobenzyl)-2-(hexahydro-azepin-4-yl)-1-(2H)-phthalazinone×HBr in 60 ml of dioxane heated to 50° C. Subsequently there were dropped in with stirring 3.8 grams (0.037 mole=5.2 ml) of triethylamine and 2.9 grams (0.015 mole) of 2-bromoethyl benzene and the mixture stirred for 9 hours at 90° C. After cooling the precipitated salt was filtered off with suction and the solution concentrated on a rotary evaporator. The brown oily residue was chromatographed over a silica

gel column (elution medium: diethyl ether/methanol=70:30) for rectification. The desired fractions were combined and the solvent distilled off in a vacuum. The residue was treated with 5 ml of isopropanol/HCl and 30 ml of ether. The hydrochloride thereupon precipitated as a viscous mass. The supernatant solution was decanted, the remaining residue dissolved in a little methyl-ethyl ketone and ether added until slight turbidity. The hydrochloride which crystallized out overnight at room temperature was filtered off with suction, washed with methyl-ethyl ketone and dried in a vacuum. M.P. of the hydrochloride 173°–176° C. Yield 2.6 grams (34%).

EXAMPLE 3

4-(4-Chlorobenzyl)-2-(hexahydro-1-methoxyethyl-azepin-4-yl)-1-(2H)-phthalazinone (formula I, R=methoxyethyl)

6 grams (0.013 mole) of 4-(4-chlorobenzyl)-2-(hexahydroazepin-4-yl)-1-(2H)-phthalazinone× HBr were stirred together with 3.6 grams (0.026 mole) of K_2CO_3, 7.4 grams (0.078 mole=7.1 ml) of 2-chloroethyl methyl ether and 30 ml of dimethylacetamide for 2½ hours at an oil bath temperature of 120° C. Subsequently the mixture was cooled to room temperature and filtered off with suction from the insolubles. The solution was concentrated in a vacuum and the brownish oil obtained chromatographed by means of a silica gel column (elution agent: CH_2Cl_2/CH_3OH=90:10). The desired fractions were combined and the solvent distilled off on the rotary evaporator. The oily residue was made acid with isopropanol/HCl. The hydrochloride was precipitated as a viscous mass by addition of ether. After decanting off the supernatant solution the residue was triburated with methyl ethyl ketone at boiling heat, whereby the desired hydrochloride was obtained as a crystalline product. M.P. 194°–197° C. Yield: 1.8 grams (28%).

EXAMPLE 4

4-(4-Chlorobenzyl)-2-(hexahydro-1-allylazepin-4-yl)-1-(b 2H)-phthalazinone (formula I, R =allyl)

There were added to a solution of 6 grams (0.013 mole) of 4-(4-chlorobenzyl)-2-(hexahydroazepin-4-yl)-1-(2H)-phthalazinone×HBr in 60 ml dioxane heated to 50° C., 3.2 grams (0.003 mole=4.4 ml) of triethylamine and subsequently with stirring 1.6 grams (0.013 mole=1.15 ml) of allyl bromide. After the addition was carried out the mixture was stirred for an additional 2 hours at a temperature of 60° C. Subsequently the reaction mixture was filtered and the solvent distilled off in a vacuum. The oily residue obtained was dissolved in isopropanol/HCl at room temperature and this solution treated with ether up to slight turbidity. The hydrochloride crystallized out overnight. This was filtered off with suction followed by washing with isopropanol and dried in a drying oven. M.P. of the hydrochloride 123° C. Yield: 2.7 grams (45%).

The compounds of the invention show a good antiallergic and antihistamine action with the allergic and non-allergic setting free of histamine on rabbit leucocytes and rat peritoneal mast cell. The non-allergic setting free of histamine is released by a material which opens up the calcium channels in the mast cell membranes or leucocyte membranes and through this effects a release of histamine (for example Ca-Inophor A 23187).

For example there is obtained in the above-mentioned experimental method at a dosage of 0.3 mg/kg body weight with guinea pigs a 50% checking of the asthma attacks.

This antiallergic action is comparable with the action of the known medicine "Azelastine". The lowest effective dosage in the above-mentioned animal experiments for example is

0.03 mg/kg orally

0.01 mg/kg intravenously

As a general dosage range for the action (animal experiments as above) is for example

0.3–3.0 mg/kg orally

0.1–1.0 mg/kg intravenously

Indication for which the compounds of the invention can be taken in consideration: allergic asthma, allergic rhinitis.

The pharmaceutical preparations generally contain between 0.1 to 10, preferably up to 5 mg of the active components.

The dispensation for example can be carried out in the form of tablets, capsules, pills, dragees, plugs, salves, gels, creams, powders, dust powders, aerosols or in liquid form. As liquid forms of use there can be used for example oily or alcoholic or aqueous solutions, as well as suspensions and emulsions. Preferred forms of use are tablets which contain between 0.5 and 5 mg or solutions which contain 0.1 to 3% of an active material.

The individual dosages of the active components according to the invention can be for example:

(a) in oral forms of medicine between 0.5–5 mg, preferably 2 mg,

(b) in parenteral forms of medicine (for example intravenous, intramuscular) between 0.1–1 mg, preferably 0.5 mg,

(c) in forms of medicines for inhalation (solutions or aerosols) between 0.5 and 2 mg),

(d) in forms of medicine for local application to the skin and mucous membranes (for example in the form of solution, lotions, emulsions, salves, etc) between 1 and 5 mg, preferably 2 mg.

(The doses in each case are based on the free base).

For example, there can be reocmmended 1 to 2 tablets having an active material content of 0.5 to 5 mg three times a day or for example in intravenous injection an ampoule having a content of 1 to 2 ml with 0.5 to 5 mg of material one to two times a day. The maximum daily dosage in oral dispensation should not exceed 10 mg.

In treating dogs and cats the individual dosage orally is generally between approximately 0.5 and 5.0 mg/kg body weight; the parenteral dosage is between approximately 0.3 and 3.0 mg/kg body weight.

In treating horses and cattle the individual oral dosage is generally between approximately 0.3 and 3.0 mg/kg body weight.

The acute toxicity of the compounds of the invention on the mouse (expressed by LD50 mg/kg, method of Miller and Tainter: Proc. Soc. Exper. Biol. and Med. Vol. 57 (1944) page 261) for example in oral application is above 200 mg/kg.

The medicines can be used in human medicine, verterinary medicine as well as in agriculture alone or in admixture with other pharmacologically active materials.

Examples of Galenical Preparation

EXAMPLE I

(Capsules)

50 grams of active material according to Example 1 were mixed with 350 grams of microcrystalline cellulose, 590 grams of lactose and 10 grams of magnesium stearate. The mixture was filled into size 3 hard gelatin plug capsules in each can there being used an amount of 100 mg.

EXAMPLE II

(Tablets)

50 grams of active material according to Example 1 were mixed with 350 grams of microcrystalline cellulose, 590 grams of lactose and 10 grams of magnesium stearate. This mixture was pressed into bicomex tablets having a weight of 100 mg, a diameter of 6 mm and a radius of curvature of 5 mm.

The tablets can subsequently be coated according to customary process with a gastric juice permeable or soluble film.

EXAMPLE III

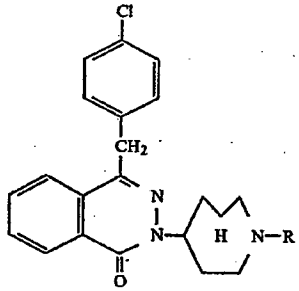
(Ampoules For Injection and Inhalation)

10 grams of active material according to Example 1 were dissolved in 400 ml of ethanol and the solution filled up to 4 liters by addition of water for injection purposes. The solution was filtered sterilely through a membrane filter of suitable pore size. The filtrate was filled under aseptic conditions to 2 ml in ampoules. The ampoules were subsequently sterilized for 20 minutes in superheated steam at 121° C. for 20 minutes.

An ampoule contains 5 mg of active material in 2 ml of solution.

What is claimed is:

1. A substituted benzylphthalazinone. of the formula



I

wherein R is a benzyl group, a phenylethyl group, a methoxy-ethyl group or an allyl group or a physiologically compatible acid addition salt thereof.

2. A substituted benzylphthalazinone according to claim 1 wherein R is a benzyl group.

3. A substituted benzylphthalazinone according to claim 1 wherein R is a phenylethyl group.

4. A substituted benzylphthalazinone according to claim 2 wherein R is a methoxyethyl group.

5. A substituted benzylphthalazinone according to claim 1 wherein R is an allyl group.

6. A pharmaceutical composition for suppressing the liberation of histamine comprising an effective antiallergic, antihistaminic amount of a compound according to claim 1 and a pharmaceutical adjuvant.

7. A process of supressing the liberation of histamine comprising administering to a mammal an amount of a compound of claim 1 effective for such purpose.

8. A process according to claim 1 where R is a benzyl group.

9. A process according to claim 6 where R is a phenethyl group.

10. A process according to claim 6 where R is a methoxyethyl.

11. A process according to claim 6 where R is an allyl group.

* * * * *

United States Patent [19]
Thomas et al.

[11] **Patent Number: 4,769,369**
[45] **Date of Patent: * Sep. 6, 1988**

[54] **ANTI-ALLERGY 1(2H)-PHTHALAZINONES**

[75] Inventors: **Telfer L. Thomas**, Pittsford; **Lesley A. Radov**, Penfield, both of N.Y.

[73] Assignee: **Pennwalt Corporation**, Philadelphia, Pa.

[*] Notice: The portion of the term of this patent subsequent to May 12, 2004 has been disclaimed.

[21] Appl. No.: **931,279**

[22] Filed: **Nov. 14, 1986**

[51] Int. Cl.[4] C07D 237/32; C07D 401/12; C07D 403/12; A61K 31/50

[52] U.S. Cl. 514/234.5; 514/248; 544/237; 544/116

[58] Field of Search 544/237, 116; 514/222, 514/232, 234, 248

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,665,181 5/1987 Thomas et al. 544/237

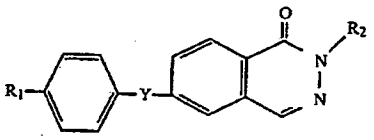
FOREIGN PATENT DOCUMENTS

2632656 2/1977 Fed. Rep. of Germany .

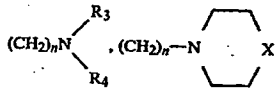
Primary Examiner—Mark L. Berch

[57] **ABSTRACT**

Novel 1 2(H)-phthalazones are disclosed along with a method of treating either allergic rihinitis or bronchial asthma by the administration to a mammal an effective amount of a compound of the formula:



wherein
R_1 is hydrogen, hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio,
R_2 is



or 1-pyrrolidinyl,
R_3 and R_4 are independently hydrogen or C_1–C_4 alkyl,
X is CH_2, O or NR_5,
Y is ethylene or ethenylene,
R_5 is hydrogen or C_1–C_4 alkyl,
n is 2, 3 or 4,
and all stereoisomeric forms and pharmaceutical acceptable addition salts thereof.

14 Claims, No Drawings

ANTI-ALLERGY 1(2H)-PHTHALAZINONES

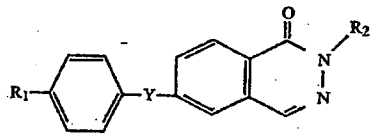
BACKGROUND OF THE INVENTION

Allergic rhinitis (e.g., hayfever) and bronchial asthma can result from the inhalation of specific antigenic materials (allergens) by susceptible individuals who respond with Immunoglobulin E (IgE)-mediated reactions. The interaction of the allergen with the IgE molecule, on the surface of a mast cell, leads to the release of a variety of bio-chemical mediators presumed to be responsible for symptoms such as vasodilation, edema, increased mucus secretion, cellular recruitment and increased capillary permeability. In addition to histamine, other mediators, such as the sulfidopeptide leukotrienes LTC_4 and LTD_4, are likely to be involved in the manifestation of many of these symptoms.

Drugs which are useful in the treatment of the above-mentioned allergic responses are believed to exert their effects by inhibiting mast cell mediator release, either by blocking the effects of these mediators on their targer cell or by relaxing airway smooth muscle. Compounds that either inhibit LTC_4 induced contractions of the guinea pig ileum, inhibit edema in the rat anaphalaxis test, or inhibit the wheal reaction in the rat alergic mediator induced thermal vascular permeability test, are expected to be useful in the treatment of bronchial asthma and allergic rhinitis.

SUMMARY OF THE INVENTION

The present invention is, in part, a compound of the formula I,

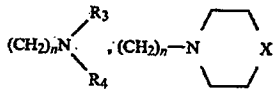


I

wherein

R_1 is hydrogen, hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio,

R_2 is



or 1-pyrrolidinyl,

R_3 and R_4 are independently hydrogen or C_1–C_4 alkyl,

X is CH_2, O or NR_5,

Y is ethylene or ethenylene,

R_5 is hydrogen or C_1–C_4 alkyl, and

n is 2, 3 or 4,

and all stereoisomeric forms and pharmaceutically acceptable addition salts thereof, provided that either

(1) R_1 is C_1–C_4 alkylthio;

(2) X is O or NR_5; or

(3) R_1 is C_1–C_4 alkylthio and X is O or NR_5.

In a subgeneric aspect, the invention is a compound of formula I as defined in the preceding paragraph, but R_1 is limited to hydroxyl, C_1–C_4 alkoxy or C_1–C_4 alkylthio.

The invention is, in part, the following novel 1(2H)-phthalazinones:

trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[2-(diisopropylamino)ethyl]phthalazin-1(2H)-one hydrobromide,

trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-piperidinopropyl)phthalazin-1(2H)-one hydrobromide,

trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(methylamino)propyl]-phthalazin-1(2H)-one hydrobromide,

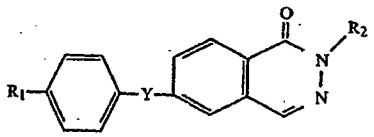
trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[2-(dimethylamino)-ethyl]-phthalazin-1(2H)-one hydrobromide,

trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-aminopropyl)phthalazin-1(2H)-one hydrobromide,

trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[4-(dimethylamino)butyl]-phthalazin-1(2H)-one bromide, and

cis-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]-phthalazin-1(2H)-one cyclohexylsulfamate.

The invention is also, in part, a method of treating either allergic rhinitis or bronchial asthma which comprises the administration to a mammal in need of such treatment of an effective amount of a compound of the formula I,

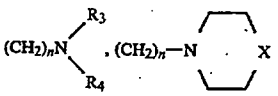


I

wherein

R_1 is hydrogen, hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio,

R_2 is



or 1-pyrrolidinyl,

R_3 and R_4 are independently hydrogen or C_1–C_4 alkyl,

X is CH_2, O or NR_5,

Y is ethylene or ethenylene,

R_5 is hydrogen or C_1–C_4 alkyl,

n is 2, 3 or 4,

and all stereoisomeric forms and pharmaceutically acceptable addition salts thereof. These compounds of the formula I inhibit LTC_4-induced contractions of the guinea pig ileum [in a test described below], inhibit edema in the rat anaphalaxis test described below and inhibit the wheal reaction in a rat allergic mediator induced dermal vascular permeability test described below. As a result, these compounds of formula I are expected to be useful in the treatment of bronchial asthma and allergic rhinitis in mammals, including humans.

In a subgeneric aspect, the invention is a method as defined in the preceding paragraph, but R_1 is limited to hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio.

The preferred 1(2H)-phthalazinones of formula I are those wherein,

R_1 is methoxy,

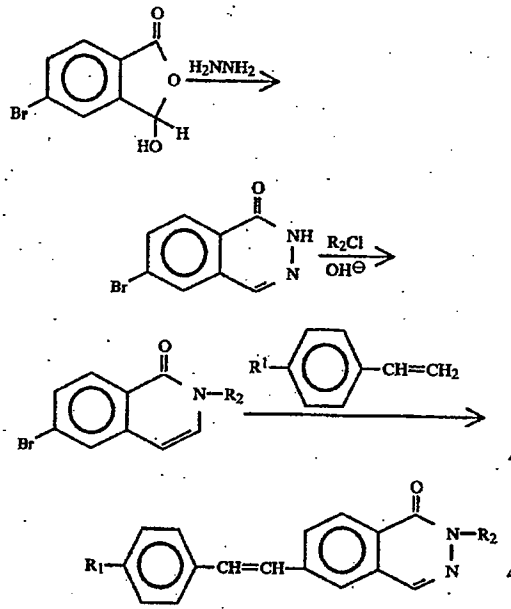
and R_2 is 3-(dimethylamino)propyl, 2-(dimethylamino)ethyl, 4-(dimethylamino)butyl, 3-piperidinopropyl, or 3-morpholinopropyl and the stereoisomeric form is the trans isomer.

The preferred salts are acid addition salts of inorganic acids such as hydrogen chloride, hydrogen bromide, sulfuric acid, or organic acids such as acetic, lactic, maleic, fumaric, malic, succinic, tartaric and methanesulfonic acids.

Methods of Preparation

Methods for preparing compounds of Formula I and appropriate intermediates are disclosed in U.S. patent application Ser. No. 611,310, filed on May 17, 1984, U.S. Pat. No. 4,665,181 (named inventors were Telfer Lawson Thomas and Leslie Ann Radov) which application is incorporated by reference here. In addition, an alternative route to the compounds of Formula I is shown in Scheme I.

Scheme I



5-Bromo-3-hydroxyphthalide is reacted in alcoholic solution with hydrazine to give 6-bromophthalazin-1(2H)-one which in turn is reacted with the appropriate (dialkylamino)alkylhalide in a polar solvent such as DMSO in the presence of a base such as KOH to give the 2-(dialkylaminoalkyl)-6-bromophthalazin-1(2H)-one. The styryl group is then attached by reacting the 6-bromo-2-substituted-phthalazin-1(2H)-one with styrene or 4-methoxystyrene in solvents such as DMSO or acetonitrile or mixtures thereof, in the presence of the reagents tri(o-tolyl)phosphine and palladium acetate to give the 6-[2-(phenyl or 4-methoxyphenyl)ethenyl]-2-[(dialkylamino)-alkyl]phthalazin-1(2H)-one. Specific methods for preparing the compounds of this invention are disclosed in the examples.

Formulations

For pharmaceutical purposes, the compounds of this invention can be administered to warm-blooded animals perorally or parenterally as active ingredients in customary dosage unit compositions. These compositions consist essentially of a dosage unit form containing the active ingredient and at least one inert pharmaceutical carrier. Dosage unit forms contemplated by the present invention include tablets, capsules, solutions, suspensions, lozenges, coated pills and parenteral compositions such as intramuscular, intravenous or intradermal preparations. Sustained release dosage forms are also contemplated where the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to mdify the release properties of the resin.

The quantity of active ingredient administered in such dosage forms can vary over a wide range depending upon the mode of administration, the size and weight of the patient and whether the nature of the treatment is prophylactic or therapeutic in nature. In general dosage unit forms contain from about 5 mg to 100 mg of the active ingredient and in man the dose is administered from 1 to 4 times daily. The total daily dosage will be from about 5 mg to 500 mg although lower and higher amounts can be used. A preferred total daily dose would be from 10 mg to 100 mg of active ingredient. p Guinea Pig Ileum Test

The methodology for determining the degree of inhibition of LTC_4 induced contractions of the guinea pig ileum by the compounds of formula I is described below and the results, expressed as the micromolar concentration required to inhibit the contraction by 50 percent, are given in Table I.

Four replicate, small pieces of guinea pig ileum were suspended in Kreb's physiological salt solution in a 10 ml tissue bath to a gram tension of approximately 1.0. These pieces of tissue were then chemically stimulated with 6 microliters of purified leukotriene C_4 (LTC_4) yielding a final concentration in the bath of 6 nanomoles. Responses (tissue contraction) were measured isometrically using a Harvard transducer and a Beckman recorder. Upon addition of the LTC_4, the tissue was allowed to sit for approximately 15–30 minutes to reach maximal stimulation. The test compound dissolved in a maximum volume of 100 microliters of either saline, dimethylsulfoxide or ethanol was then added to the tissue preparation and the change in gram tension was recorded.

TABLE I

Inhibition of LTC_4-Induced Guinea Pig Smooth Muscle Contractions	
Test Compound-Title Compound of Example No.:	IC_{50} (μm):
II	3.4
III	16.6
IV	0.1
VI	16.8
IX	10
X	10.5
XI	10
XII	13.6
XIV	31.6

Rat Anaphylaxis Test

In the rat anaphylaxis test, groups consisting of 15–20 rats are intraperitoneally sensitized on day zero with 500 μg of bovine serum albumin-absorbed alum admixed with 2×10^{10} killed Bordatella pertussis vaccine organisms. Fourteen days later, the test compound suspended in 0.5 to 1.0 ml of 1% Cleargel or saline (0.85% NaCl in H_2O) is administered ip or po and, one hour later, the right hind paw is injected subcutaneously with

100 μg of bovine serum albumin dissolved in 0.1 ml of saline. The paw volume is measured using a mercury plethysmometer prior to drug administration and 90 minutes post antigenic challenge. The present inhibition of edema is calculated as the difference in volume between the control and drug treated groups, divided by the control volume, and then multiplied times 100. The positive control drug, theophylline (90 mg/kg, po) is included in each assay. Statistical analysis of the data is done using an analysis of variance program. See Tables 2 and 3 for results obtained with this test.

In Tables 2 and 3, and elsewhere in this application, PR 948–257C stands for trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]-phthalazin-1(2H)-one hydrobromide.

TABLE 2

Effect of Intraperitoneal Administration of PR 948-257C on the Active Anaphylaxis Response in Male, Sprague Dawley Rats[a]

Group	N	Dose (mg/kg)	Paw Volume[c] Mean ± S.E.	% Inhibition
Vehicle	20	—	3.8 ± 2.3	—
Theophylline[b]	17	90	0.9 ± 0.7*	76
PR 948-257	20	100	0.4 ± 0.8*	91
	20	75	0.7 ± 0.8*	83
	20	50	1.7 ± 1.3*	56
Vehicle	20	—	4.3 ± 2.6	—
Theophylline[b]	20	90	0.4 ± 0.6*	92
PR 948-257	20	25	1.9 ± 1.4*	55
	20	12.5	2.1 ± 1.8*	52
	20	6.25	2.2 ± 1.9*	48
Vehicle	20	—	4.3 ± 2.3	—
Theophylline[b]	29	90	0.5 ± 0.5*	87
PR 948-257	19	6	3.7 ± 2.6	12
	19	4	4.9 ± 2.3	+14
	20	2.5	4.7 ± 2.8	+11

[a]The animals were intraperitoneally sensitized with 500 ug of bovine serum albumin (BSA) 14 days prior to an intraplantar paw challenge with 100 ug of BSA. The test compounds were administered one hour prior to the BSA challenge.
[b]Theophylline was orally administered.
[c]The change in paw volume is recorded as the difference between the left uninjected and right uninjected paw volume of the same animal.
*Statistically significant decrease from control values; $p < .05$, using the analysis of variance test.

TABLE 3

The Effect of Oral Administration of PR 948-257C on the Active Anaphylaxis Response of Male, Sprague Dawley Rats[a]

Group	N	Dose (mg/kg)	Paw Volume ± S.E. mm of Hg[b]	% Inhibition
Saline	20	—	3.60 ± .6	—
Theophylline	20	90	0.65 ± .2*	82
PR 948-257C	20	100	1.65 ± .36*	54
	19	75	2.26 ± .32	37
	20	50	3.10 ± .55	14

[a]The animals were intraperitoneally sensitized with 500 ug of bovine serum albumin (BSA) 14 days prior to an intraplantar paw challenge with 100 ug of BSA. The test compounds were administered one hour prior to the BSA challenge.
[b]The change in paw volume is recorded as the difference between the left uninjected and right injected paw volume of the same animal.
*Statistically significant decrease from control values; $p \leq .01$ using the analysis of variance test.

Rat Allergic Mediator Induced Dermal Vascular Permeability Test

In this test, groups of ten male rats are intraperitoneally or perorally administered 0.5 ml to 1.0 ml saline solution of either the test compound or positive reference standard cyproheptadine (1 mg/kg) one hour prior to an intravenous injection of 1 ml of a 0.5% solution of Evan's blue dye into naive animals. Ten minutes later, the animals are challenged by intradermally injecting 0.1 ml of a water solution of either serotonin (1 μg/ml), histamine (20 μg/ml) or bradykinin (10 μg/ml) into separate sites on the back. Five minutes following challenge the animals are killed, the skin retracted, and the mean diameter of the blue wheal and flare reaction is calculated as the difference in mean diameter between a saline control and the drug treated group, divided by the control diameter, and then multiplied times 100. Statistical analysis of the data is done using a Student T-test program. See Tables 4 (ip administration of test compound) and 5 (po administration of test compound) for results obtained with the rat allergic mediator induced dermal vascular permeability test. (Set: Serotonin; His: histamine; Bk: bradykinin)

TABLE 4

Compound	N	Dose (mg/kg)	Wheal Measurement (mm) and Standard Errors Ser	His	Bk	% Inhibition Ser	His	Bk
Control	10	—	11.1 ± 0.2	11.2 ± 0.2	10.9 ± 0.2	—	—	—
Cyproheptadine	10	1	2.8 ± 0.9***	0.8 ± 0.8***	4.3 ± 4.0***	74.8	92.9	60.6
PR 948 257C	10	50	3.5 ± 1.1***	2.7 ± 1.1***	2.8 ± 1.1***	68.5	75.9	74.3
PR 948-257C	10	25	5.4 ± 1.0***	5.6 ± 1.0***	5.7 ± 1.1***	51.4	50.0	47.7
PR 948-257C	10	12.5	8.2 ± 1.0**	8.2 ± 1.0**	7.4 ± 1.0***	26.1	26.8	32.1

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

TABLE 5

Compound	N	Dose (mg/kg)	Wheal Measurement (mm) and Standard Errors Ser	His	Bk	% Inhibition Ser	His	Bk
Control	10	—	10.3 ± 0.4	10 ± 0.3	9.1 ± 0.3	—	—	—
Cyproheptadine	10	1	0.5 ± 0.5***	0 ± 0***	1.2 ± 0.8***	95.1	100	86.8
PR 948-257C	10	12.5	7.9 ± 0.4***	8.3 ± 0.3***	8.0 ± 0.4*	23.3	17	12.1
PR 948-257C	10	25	5.9 ± 0.7***	4.3 ± 1.0***	4.7 ± 0.8***	42.7	57	48.4

TABLE 5-continued

Compound	N	Dose (mg/kg)	Wheal Measurement (mm) and Standard Errors Ser	His	Bk	% Inhibition Ser	His	Bk
PR 948-257C	10	50	4.0 ± 1.1***	2.9 ± 1.2***	3.3 ± 1.1***	61.1	71	63.8

*p < 0.05
**p < 0.01
***p < 0.001

EXAMPLES

Example I

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[2-(diisopropylamino)-ethyl]phthalazin-1(2H)-one hydrobromide

Step a

6-Bromophthalazin-1(2H)-one

5-Bromo-3-hydroxyphthalide (49 gm) was slurred in 200 ml isopropanol. Hydrazine (20 ml) was added and the mixture refluxed for 2 hours. The reaction mixture was allowed to cool and the product filtered off, washed with isopropanol and dried. The product weighed 46.8 gm and melted at 280°–283° C.

Step b

6-Bromo-2-[2-(diisopropylamino)ethyl]phthalazin-1(2H)-one

6-Bromophthalazinone (11.2 gm, 0.05 mole) was slurried in 80 ml dimethylsulfoxide. To this was added 22 ml 45% KOH (0.25 mole). After stirring 10 minutes 16 gm 2-(diisopropylamino)ethyl chloride hydrochloride was added and the mixture stirred for 18 hours. A water bath was used to moderate the slightly exothermic reaction (temperature <=25°). Water (100 ml) was added to the reaction mixture, which was then stirred another hour.

The product was filtered, washed to colorless washings with water and dried. The product weighed=17.7 gm. Tlc (40% ethyl acetate in cyclohexane on an ammonia treated silica plate) showed a single product R_f=0.59; no starting material, R_f=0.23, was visible. Two barely visible trace spots, R_f=0.36 and 0.32 were also present.

Recrystallization of a 6.3 gm sample from 35 ml methoxyethanol yielded 3.8 gm of product showing a single spot on tlc.

Step c

Trans-6-[2-(4-methoxyphenyl)ethyl]-2-[2-(diisopropylamino)ethyl]phthalazin-1(2H)-one hydrobromide

6-Bromo-2-[2-(diisopropylamino)ethyl]phthalazin-1(2H)-one (10.6 gm, 0.03 mole, prepared in Example I) was stirred into 16 ml DMSO plus 16 ml acetonitrile. To the resulting mixture was added 4.5 gm 4-methoxystyrene (0.033 mole), 0.1 gm tri(o-tolyl)phosphine, and 0.02 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. Allowed to cool to about 60° C. and diluted with 60 ml of isopropanol. Stirred for an hour, filtered, washed to colorless washings with isopropanol and dried. The product weighed 11.3 gm. After recrystallization from 80 ml 1:1:ethanol:water the product weighed 10.0 gm and melted at 251°–252° C.

EXAMPLE II

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-piperidinopropyl)phthalazin-1(2H)-one hydrobromide

6-Bromo-2-(3-piperidinopropyl)phthalazin-1(2H)-one (7.2 gm, 0.018 mole) (prepared as in Example I, except that 1-(3-chloropropyl)piperidine hydrochloride was substituted for the 2-(diisopropylamino)ethyl chloride hydrochloride) was stirred into 10 ml DMSO plus 10 ml acetonitrile. To the resulting mixture was added 2.8 gm 4-methoxystyrene (0.021 mole), 0.1 gm tri(o-tolyl)phosphine, and 0.02 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. Allowed to cool to about 60° C. and diluted with 40 ml of isopropanol. Stirred for an hour, filtered, washed to colorless washings with isopropanol and dried. The product weighed 8.6 gm. After recrystallization from 50 ml methoxyethanol the product weighed 6.4 gm and melted at 248°–250° C.

Example III

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[2-(dimethylamino)ethyl]-phthalazin-1(2H)-one hydrobromide

6-Bromo-2-[2-(dimethyamino)ethyl]phthalazin-1(2H)-one (7.2 gm, 0.018 mole) (prepared as in Example I, except that 2-(dimethylamino)ethyl chloride hydrochloride was substituted for the 2-(diisopropylamino)ethyl chloride hydrochloride) was stirred into 16 ml DMSO plus 16 ml acetonitrile. To the resulting mixture was added 4.5 gm 4-methoxystyrene (0.033 mole), 0.1 gm tri(o-tolyl)phosphine, and 0.02 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. Allowed to cool to about 60° C. and diluted with 60 ml of isopropanol. Stirred for an hour, filtered, washed to colorless washings with isopropanol and dried. The product weighed 10.7 gm. After recrystallization from 240 ml methoxyethanol the product weighed 6.4 gm and melted at 265°–267° C.

Example IV

Trans-6-[2-(4-methioxyphenyl)ethenyl]-2-(2-morpholinoethyl)phthalazin-1(2H)-one hydrobromide

6-Bromo-2-(2-morpholinoethyl)phthalazin-1(2H)-one (10.1 gm, 0.03 mole) (prepared as in Example I, except that 2-morpholinoethyl chloride hydrochloride was substituted for the 2-(diisopropylamino)ethyl chloride hydrochloride) was stirred into 16 ml DMSO plus 16 ml acetonitrile. To the resulting mixture was added 4.5 gm 4-methoxystyrene (0.033 mole), 0.1 gm tri(o-tolyl)phosphine, and 0.02 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. Allowed to cool to about 60° C. and diluted with 60 ml of isopropanol. Stirred for an hour, filtered, washed to colorless washings with isopropanol and dried. The product weighed 11.9 gm. After recrystallization from

40 ml ethanol plus 30 ml water the product weighed 9.2 gm and melted at 254°–256° C.

Example V

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(1-piperazino)propyl]phthalazin-1(2H)-one

6-Bromo-2-(3-piperazinopropyl)phthalazin-1(2H)-one (2.1 gm, 0.0062 mole) (prepared as in Example I, except that 3-piperazinopropyl chloride hydrochloride was substituted for the 2-(diisopropylamino)ethyl chloride hydrochloride) was stirred into 4 ml DMSO plus 4 ml acetonitrile. To the resulting mixture was added 1 gm 4-methoxystyrene (0.0075 mole), 0.05 gm tri(o-tolyl)phosphine, and 0.01 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. Allowed to cool to about 60° C. and diluted with 20 ml of isopropanol. Stirred for 2 hours, filtered, washed to colorless washings with isopropanol and dried. The product weighed 1.4 gm. and melted at 206°–209° C.

Example VI

6-[2-(4-methoxyphenyl)ethyl]-2-[3-(dimethylamino)-propyl]phthalazin-1(2H)-one

6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]phthalazin-1(2H)-one (9 gm) was dissolved in 200 ml methoxyethanol and reduced on a Parr hydrogenator using 1 gm of 10% palladium on carbon as catalyst. Reduction was complete within 2 hours. The catalyst was filtered off, the solvent removed on a rotary evaporator and the residue recrystallized from 500 ml of isoproanol. The product weighed 8.3 gm and melted at 201°–203° C.

Example VII

Trans-6[2-(4-methoxyphenyl)ethenyl]-2-[3-(methylamino)propyl]phthalazin-1(2H)-one hydrobromide

Trans-6-[2-(4-Methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]phthalazin-1(2H)-one (8.9 gm, 0.024 mole) in 150 ml toluene was treated with 27 ml 12% phosgene in toluene and stirred for 7 days. The solvent was removed and the residue recrystallized from 25 ml carbon tetrachloride plus 15 ml toluene, yielding 5.4 gm of the chlorocarbonyl intermediate.

This intermediate was heated in 125 ml water at about 90° C. for 30 minutes. The solution was clarified, basified with potassium carbonate and extracted into ethyl acetate. The solvent was removed and the residue dissolved in 30 ml ethanol and acidified with 3 ml 30% HBr in acetic acid. The product was allowed to crystallize, filtered and washed with isopropanol. The purified product weighed 3.8 gm and melted at 256°–258° C.

Example VIII

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-aminopropyl)phthalazin-1(2H)-one hydrobromide

Step a

6-Bromo-2-(3-carboxypropyl)phthalazin-1(2H)-one

To a slurry of 56 gm 6-bromophthalazin-1(2H)-one (0.25 mole) in 600 ml DMSO was added 110 ml 45% KOH followed by 58.5 gm ethyl 4-bromobutyrate. The temperature of the mildly exothermic reaction was moderated with a water bath (ca. 25° C.) and was stirred for 20 hours. Ethanol (750 ml) was added, then the mixture was acidified with 125 ml concentrated HCl, diluted with 2500 ml water over about 30 minutes, stirred an additional 30 minutes, filtered, washed with water and isopropanol and dried. The product weighed 63.6 gm. A tlc of the product showed product, R_f=0.43 plus a trace of starting material, R_f=0.63.

Step b

6-Bromo-2-(3-aminopropyl)phthalazin-1(2H)-one

6-Bromo-2-(3-carboxypropyl)phthalazin-1(2H)-one (9.3 gm, 0.03 mole, prepared in Example XIV) was dissolved in 185 ml acetone by adding 4.7 ml triethylamine (0.0335 mole). The slightly cloudy solution was clarified, cooled to <10° C. and 3.8 gm methyl chloroformate (0.04 mole) was added over about 5 minutes. Stirred with cooling for another 30 minutes, then added a solution of 4 gm sodium azide (0.062 mole) in 25 ml water. Stirred for 30 minutes, added to 400 ml ice water and extracted three times with 80 ml methylene dichloride. This solution was dried, 4 ml of trifluoroacetic acid was added, and the solution refluxed for 18 hours. Methanol (100 ml) was added and the solution shaken with dilute potassium carbonate solution to free the base. The resulting solution was acidified with 10 ml of 30% HBr in acetic acid, diluted with 900 ml ether, filtered and washed with ethyl acetate. The product weighed 6.3 gm and showed a single spot on tlc, R_f=0.28 (using 10% methanol in chloroform on an ammonia treated silica plate).

Step c

6-Bromo-2-[3-[(t-butoxycarbonyl)amino)propyl]phthalazin-1(2H)-one

6-Bromo-2-(3-aminopropyl)phthalazin-1(2H)-one (13.6 gm, prepared as in Example XV) was dissolved in a mixture of 130 ml chloroform and 60 ml t-butanol. Triethylamine (5.8 ml) and 9.1 gm of di(t-butyl)dicarbonate were added and the solution was allowed to stand for 5 days in the dark. The solution was added to a solution of 15 gm citric acid in 380 ml water and stirred for a few minutes. The chloroform layer was separated and the aqueous layer extracted twice more with 75 ml chloroform. The combined chloroform extracts were extracted twice with 75 ml water and once with 75 ml potassium carbonate solution. The solution was dried, the solvent removed and the residue slurried in 110 ml of cyclohexane for 1 hour. The product was filtered off and washed with cyclohexane. It weighed 12.7 gm and melted at 130°–132° C.

Step d

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-aminopropyl]phthalazin-1(2H)-one hydrobromide

A mixture of 9.1 gm 6-Bromo-2-[3-[(t-butoxycarbonyl)amino]propyl]phthalazin-1(2H)-one (0.0238 mole, prepared as described above), 3.7 ml 4-methoxystyrene (0.028 mole), 18 ml DMSO, 18 ml acetonitrile, 3 gm triethylamine (0.03 mole), 0.15 gm tri-(o-tolyl)phosphine (0.0005 mole) and 0.03 gm palladium acetate (0.00013 mole) were refluxed together for 20 hours. It was diluted with 40 ml isopropanol after allowing to cool to about 80° C. The solution was added to 200 ml water and 200 ml ethyl acetate shaken well, and the organic layer separated. The water layer was extracted twice more with 100 ml ethyl acetate, the organic solution washed with water, dried and concentrated to dryness. The crude product (weight=9.3 gm) was recrystallized from 45 ml isopropanol, yielding 6.6 gm of

pure product having an R_f of 0.26 using 40% ethyl acetate in cyclohexane on a silica plate.

The protecting group was removed by slurrying in 130 ml isopropanol containing 160 ml 30% HBr in acetic acid. The product was filtered off and washed with isopropanol. It weighed 5.1 gm and showed a single spot on tlc. After recrystallization from 65 ml 95% ethanol plus 10 ml water it weighed 3.9 gm and melted at 291°–293° C.

Example IX

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[4-dimethylamino)butyl]phthalazin-1(2H)-one bromide

Step a

6-Bromo-2-[4-(dimethylamino)butyl]phthalazin-1(2H)-one

6-Bromo-2-(3-carboxypropyl)phthalazin-1(2H)-one (18.4 gm 0.06 mole, prepared as described above) was dissolved in a mixture of 400 ml methylene dichloride and 10 ml triethylamine. Methyl chloroformate (7.6 gm, 0.07 mole) was added, the mixture stirred for a few minutes, then the solvent removed on a rotary evaporator. The residue was dissolved in 30 ml absolute ethanol and 1.2 gm sodium borohydride (0.03 mole) was added portionwise over 1 hour. The mixture was stirred for 20 hours, diluted with 20 ml water, stirred 15 minutes, then basified with 25 ml water containing 5 ml 45% potassium hydroxide and stirred 20 hours. The solution was acidified and the product filtered off, washed with water and dried. The product weighed 7.1 gm. Work up of the filtrates allowed recovery of 9.1 gm of starting acid. bp

The alcohol above (7.1 gm, 0.024 mole) was dissolved in 75 ml pyridine and stirred with 8.6 gm p-toluenesulfonyl chloride for 6 hours at ambient temperature. The mixture was added to 225 gm ice plus 125 ml concentrated HCl and the product extracted into methylene dichloride. Removal of the solvent left 7.5 gm solid. This material was dissolved in 45 ml DMSO and 8 ml dimethylamine. After heating at 80° C. for 6 hours the mixture was allowed to cool and stand over night. It was added to 300 ml water and extracted three times with 150 ml ethyl acetate, washing each extract three times with 75 ml water. The product was then extracted from the organic solution with three 100 ml portions of dilute HCl. The acidic solution was basified, the product extracted into chloroform, dried and the solvent removed, leaving 3.1 gm of crystalline product.

Step b

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[4-dimethylamino)butyl]phthalazin-1(2H)-one hydrobromide

The procedure used was identical to that used in preparing 6-[2-4-methoxyphenyl)ethenyl]-2-[2-(dimethylamino)ethyl]phthalazin-1(2H)-one (Example III above), except that 6-Bromo-2-[4-(dimethylamino)butyl-])phthalazin-1(2H)-one was substituted for 6-Bromo-2-[2-(dimethyamino)ethyl]phthalazin-1(2H)-one. The weight of product obtained from 7.5 gm starting halide was 7.1 gm after recrystallization from 50 ml of methoxyethanol. It melted at 225°–227° C.

Example X

Cis-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-dimethylaminopropyl]phthalazin-1(2H)-one cyclohexylsulfamate

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-dimethylaminopropyl]-phthalazin-1(2H)-one (48 gm) in 7000 ml 20% isopropanol in ethanol was irradiated in a 12 liter flask with a 450 watt Hanovia ultraviolet lamp for 8 hours. The solution was concentrated to dryness and the residue slurried in 55 ml ethanol, heated to a cloudy solution, allowed to cool and filtered off the trans-isomer that had crystallized from the solution. The filtrate, which was cis-isomer contaminated with a little trans-isomer and some minor impurities, was diluted with water, basified and the product extracted into chloroform. The solution was concentrated to dryness and the residue chromatographed on a preparative liquid chromatographic apparatus using a silica column. The product was eluted with a 5:3:1:1 mixture of ethyl acetate:n-butanol:acetic acid:water giving 12.7 gm of oily product. The product was converted to the cyclohexylsulfamic acid salt using 10 gm of the acid in 70 ml of acetone. It weighed 11.6 gm and melted at about 110°–120° C.

Example XI

Trans-6-[2-[4-(methylthio)phenyl]ethenyl]-2-[3-(dimethylamino)propyl]phthalazin-1(2H)-one

6-Bromo-2-[3-(dimethylamino)propyl]phthalazin-1(2H)-one (8.5 gm) (prepared as in Example I, except that 3-(dimethylamino)propyl chloride hydrochloride was substituted for the 2-(diisopropylamino)ethyl chloride hydrochloride) was stirred into 4 ml DMSO plus 4 ml acetonitrile. To the resulting mixture was added 3.7 gm 4-methylthiostyrene, 0.2 gm tri(O-tolyl)phosphine, and 0.04 gm palladium acetate. The reaction mixture was stirred at reflux (95°–100° C.) for 24 hours. The solution was concentrated to dryness on a rotovap and the residue recrystallized from 95% ethanol yielding 5.5 gm of product melting at 210° C.

Example XII

Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]-phthalazin-1(2H)-one hydrobromide

The procedure used was identical to that used in preparing 6-[2-(4-methoxyphenyl)ethenyl]-2-[2-(dimethylamino)ethyl]phthalazin-1(2H)-one (Example III above), except that 6-Bromo-2-[3-(dimethylamino)-propyl]phthalazin-1(2H)-one was substituted for 6-Bromo-2-[2-(dimethyamino)ethyl]phthalazin-1(2H)-one. The weight of product obtained from 102 gm starting halide was 104 gm after recrystallization from 50 ml of methoxyethanol. It melted at 232°–234° C.

Example XIII

Trans-6-[2-(4-hydroxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]-phthalazin-1(2H)-one hydrochloride

Trans-6-[2-(4-Methoxyphenyl)ethenyl]-2-[3-(dimethylamino)propyl]-phthalazin-1(2H)-one (prepared as in Example XIV) (46.6 gm, 0.122 mole) and 245 gm pyridine hydrochloride were heated together with stirring at 180° C. for 7 hours. The hot melt was added to 1200 ml water and stirred over night. The product was filtered off and washed with three 400 ml portions of

water. The damp product was slurried in 350 ml of tetrahydrofuran plus 350 ml methanol, acidified with gaseous HCl, filtered and washed with ethanol. The product, which weighed 36 gm, was recrystallized from 275 ml water. Wgt=30.2 gm, mp=283°–283° C.

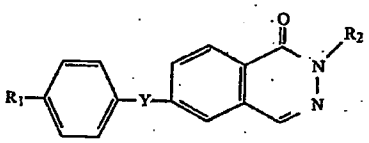
Example XIV

Trans-6-[2-(4-Hydroxyphenyl)ethenyl]-2-(2-dimethylaminoethyl)-1(2H)-phthalazinone hydrochloride

Following the procedure of Example XIII above trans-6-[2-(4-hydroxyphenyl)ethenyl]-1(2H)phthalazinone (19.8 g) and 2-dimethylaminoethyl chloride hydrochloride (17.3 g) were reacted to give the 2-(2-dimethylaminoethyl) derivative as the hydrochloride (16 g), mp 283°–285° C.

What is claimed is:

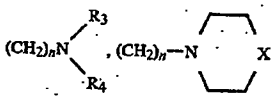
1. A compound of the formula



wherein

R_1 is hydrogen, hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio,

R_2 is



or 1-pyrrolidinyl,

R_3 and R_4 are independently hydrogen or C_1–C_4 alkyl,

X is CH_2, O or NR_5,

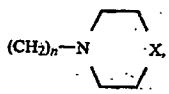
Y is ethylene or ethenylene,

R_5 is hydrogen or C_1–C_4 alkyl, and

n is 2, 3 or 4,

and all stereoisomeric forms and pharmaceutically acceptable addition salts thereof, provided that

if R_1 is other than C_1–C_4 alkylthio; then R_2 must be either;



where X is O or NR_5, or 1-pyrrolidinyl.

2. A compound as defined in claim 1 provided further that R_1 is not hydrogen.

3. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[2-diisopropylamino)-ethyl]phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

4. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-piperidinopropyl)-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

5. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(methylamino)propyl]-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

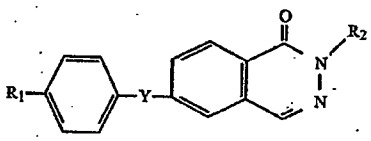
6. Trans-6-[2-(4-methoxyphenyl)ethyl)-2-[2-(dimethylamino)ethyl]-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

7. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(3-aminopropyl)phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

8. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[4-dimethylamino)butyl]-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

9. Cis-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-(dimethylaminopropyl]-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

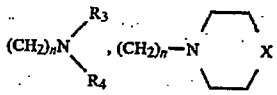
10. The method of treating either allergic rhinitis or bronchial asthma which comprises the administration to a mammal in need of such treatment of an effective amount of a compound of the formula



wherein

R_1 is hydrogen, hydroxyl, C_1–C_4 alkoxy, or C_1–C_4 alkylthio,

R_2 is



or 1-pyrrolidinyl,

R_3 and R_4 are independently hydrogen or C_1–C_4 alkyl,

X is CH_2, O or NR_5,

Y is ethylene or ethenylene,

R_5 is hydrogen or C_1–C_4 alkyl,

n is 2, 3 or 4,

and all stereoisomeric forms and pharmaceutically acceptable addition salts thereof.

11. The method of claim 10 wherein R_1 is hydroxyl, C_1–C_4 alkylthio.

12. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-(2morpholinoethyl)-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

13. Trans-6-[2-(4-methoxyphenyl)ethenyl]-2-[3-[1-piperazino)propyl]-phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

14. Trans-6-[2-[4-(methylthio)phenyl]ethenyl]-2-[3-(dimethylamino)propyl]phthalazin-1(2H)-one and pharmaceutically acceptable salts thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,769,369
DATED : September 6, 1988
INVENTOR(S) : T. L. Thomas, L. A. Radov

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 11: Insert

"C_1-C_4 alkoxy or" after the term "hydroxyl", and before the term "C_1-C_4 alkylthio".

Signed and Sealed this

Seventeenth Day of January, 1989

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks